Annotated Clinical Review of Reteplase

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PLA number:	95-1167
Sponsor:	Boehringer Mannheim
Product:	Reteplase (rPA, recombinant plasminogen activator)
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Submitted:	June 30, 1995
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1.0 Overview:

1.1 Clinical Background:

Acute myocardial infarction (AMI) is the most common cause of death in the United states. Most cases of AMI are due to the abrupt occlusion of a coronary artery by the formation of a thrombus at the site of an atherosclerotic plaque.[1] Clinical studies performed over the past several years have demonstrated that acute lysis of the occluding thrombus using plasminogen activators results in improved short term mortality and heart function. The initial studies of coronary thrombolysis utilized the infusion of thrombolytic agents directly into the occluded coronary artery. These arteriographic studies demonstrated that thrombolysis was achieved using plasminogen activating agents. Subsequently, clinical studies utilizing the intravenous administration of plasminogen activating agents showed that early mortality (death within the first few weeks after treatment) was reduced by approximately one third, from 10 to 15 percent in the era immediately before thrombolytic agents became available, to approximately 5 to 10 percent today. Thrombolytic therapy has also been shown to result in better recovery of left ventricular

1. Anderson, H., Willerson, J. Thrombolysis in acute myocardial infarction. N Engl J Med;1993:329:703-709.

function and a lower incidence of post-infarction heart failure. Four agents are currently licensed for use in the treatment of AMI:

1. streptokinase (intravenous and intracoronary administration)
   licensed for "the lysis of intracoronary thrombi, for the improvement of ventricular function, for the reduction of the incidence of congestive heart failure associated with AMI, and for the reduction of mortality when administered by either the intravenous or intracoronary route"
2. anistreplase (intravenous administration)
   licensed for "the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, and the reduction of mortality associated with AMI."
3. tissue plasminogen activator (tPA, intravenous administration)
   licensed for "the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI."
4. urokinase (intracoronary administration)
   licensed as "has been reported to lyse acute thrombi obstructing coronary arteries, associated with evolving transmural myocardial infarction. It has not been established that intracoronary administration of Abbokinase™ during evolving transmural myocardial infarction results in salvage of myocardial tissue, nor that it reduces mortality."

Reviewer's comment: The tPA indication reflects the June, 1996 revision of the tPA label.

Currently, the most commonly utilized agents are those that are administered intravenously (streptokinase, anistreplase and tPA).

During the early studies of the efficacy of coronary thrombolysis, it was recognized that coronary reocclusion by a newly formed thrombus may negate the efficacy of the initial thrombolysis. The reocclusion rate by new thrombus formation varies with the thrombolytic agent utilized for the initial thrombolysis and the adjunctive therapies. Currently, the thrombolytic agents licensed for intravenous use are generally associated with a reocclusion rates of 5 to 15%. In the initial studies of tPA, the reocclusion rate was found to be substantially increased when heparin was not utilized as an adjunctive therapy. Currently, the licensed administration for tPA includes the recommendation for the simultaneous use of heparin. Clinical studies have also suggested a benefit for the addition of heparin therapy to streptokinase thrombolysis. However, the licensed recommendations for streptokinase (as well as antistreplase) do not direct the physician to utilize heparin as adjunctive therapy.

Reviewer's comment:

In clinical practice, the adjunction use of heparin with streptokinase is common and is supported by certain clinical trial data. Clinical trials have also demonstrated mortality benefits to the addition of aspirin to thrombolytic regimens.[2] Hence, most current thrombolytic regimens include the use of aspirin. Aspirin use is not included in the directions for use for any of the currently licensed thrombolytic agents.

The major complication of thrombolysis is bleeding. Severe bleeding (requiring transfusion) rates ranged from five to ten percent for patients receiving thrombolytics in the GUSTO-1 trial.[3] In GUSTO-1 the thrombolytic regimens included the use of heparin and aspirin.

Another significant complication of coronary thrombolysis is stroke. Both hemorrhagic stroke and nonhemorrhagic stroke have been associated with thrombolysis. The stroke rates in GUSTO-1 ranged between 1.2 and 1.6 percent, with approximately half the strokes being due to intracranial hemorrhage.

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2. ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349-60.

3. The Gusto Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.

The clinical trials included in the PLA for Reteplase (rPA) were designed to assess the overall mortality effect as well as certain specific cardiac effects and to detect complications, especially those related to bleeding.

In support of the proposed indication, the sponsor submitted nine clinical study reports, including three randomized and controlled clinical studies (RAPID-1, RAPID-2, INJECT). In this document, the review of the clinical trials will be preceded by a summary of the regulatory history guiding the clinical development of thrombolytic agents and the specific guidance the FDA provided to the sponsor for the clinical testing of reteplase. The regulatory history will be followed by a summary of the clinical studies, a summary of the results from the clinical studies and an in-depth review of the phase 3 studies. This document will provide the most detail for the phase 3 clinical trials, for which the sponsor submitted clinical study reports, SAS data sets, and specific case report forms. Monitoring of the phase 3 studies was performed by the sponsor using independent contract research organizations and/or the sponsor's internal clinical research associate monitoring program. The FDA inspected selected sites involved in the phase 3 studies and verified protocol adherence, maintenance of case report forms and data reporting.

1.2 Regulatory Background: Recommendations for Thrombolytic Studies:

The Cardiovascular and Renal Drugs Advisory Committee met on December 16, 1992 and discussed areas of interest in the development of new thrombolytic agents. The following conclusions are from the minutes of the meeting:

1. "it was necessary to establish patency response as a function of dose for approval of a new molecule,
2. patency was not a sufficient surrogate for evaluating a new molecule.
3. the primary endpoint (vote 11-1) of equivalence trials should be all cause mortality.
4. There was general support for the notion that a trial would need to be large enough to conclude that the new thrombolytic should not be substantially inferior to the positive control.
5. There was also general support for the notion that the incidence of intracerebral hemorrhage would need to be known with reasonable precision.
6. There was also general support for the notion that trials should not be too large but there was recognition that they should be large enough to resolve the statistical questions just mentioned."

Certain speakers during the meeting suggested that a new thrombolytic agent should retain at least 50% of the mortality benefit of the comparator thrombolytic agent. This contention was not a recommendation of the Advisory Committee. Based upon discussions at the advisory committee meeting, the FDA subsequently recommended that Boehringer Mannheim (as well as other sponsors) evaluate new thrombolytic agents with a goal of retaining at least 50% of the mortality benefit of a comparator thrombolytic agent.

The sponsor met with the FDA on July 20, 1993 and the sponsor's submitted summary of this meeting noted that the FDA agreed: "that a new thrombolytic must be shown to preserve at least 50% of the mortality reduction effect of approved agents" and "that patency/TIMI 3 comparisons between reteplase and alteplase from the RAPID-1 and RAPID-2 trials could be included in the labeling provided the mortality study convincingly demonstrated that reteplase is effective in reducing the mortality associated with AMI."

The sponsor met with the FDA again, on April 5, 1995 and the FDA requested that the sponsor satisfy the "50% rule" on the difference in mortality rates in each trial arm (absolute mortality difference) and that analyses of the INJECT study should be performed for the entire population (patients entered within 12 hours of the onset of pain) and for the group of patients entered within 6 hours of the onset of pain. The sponsor was also told to examine the effect of mortality and safety endpoints based on weight comparisons.

•Reviewer's comment: Because of the efficacy of thrombolytics agents in the treatment of AMI, it is currently regarded as unethical to perform placebo-controlled studies to evaluate a new thrombolytic agent. Hence, sponsors and the FDA have agreed that comparative trials should be performed. The three currently licensed thrombolytics (for intravenous administration) were evaluated in placebo-controlled studies. Reteplase is the first "new" thrombolytic agent to be evaluated in solely comparative trials. The design of these comparative trials was discussed at the December 16, 1992 meeting of the

Cardiovascular and Renal Drugs Advisory Committee. The "50% rule" stems from comments made at that meeting and subsequent internal discussions. The "50% rule" implies that the new agent will retain at least 50% of the efficacy benefit of the old agent. In a trial in which a new agent is compared to an old agent and not a placebo, the clinical benefit of the old agent must be ascertained from historical controls (the "historical control assumption").[4] Once this amount of benefit (mortality of old agent - mortality of placebo) has been ascertained, the upper boundary of the new agent - old agent mortality rate (one-sided, 95% confidence interval) must not exceed 1/2 of the mortality benefit of the old agent. In general, this is a modification of an active control-equivalency trial. Even though the advisory panel stated that efficacy should not be evaluated in terms of a positive effect compared to a predicted (not active placebo) effect, the contention that a new thrombolytic should retain at least 50% of the mortality benefit of the comparator thrombolytic must be based on historical controls.

The basic statistical design of the pivotal clinical trial (INJECT) was formulated prior to the July 20, 1993 meeting with the FDA and the statistical design was not changed following that meeting. The minutes of the July 20, 1993 (formulated by the sponsor and submitted to the FDA) do not indicate that any alteration of the statistical design was necessary. In the original clinical protocol, the statistical powering of INJECT was based on hypothesis testing to detect any efficacy of rPA compared to streptokinase (SK). The null hypothesis in INJECT was: $\pi_{rPA} - \pi_{SK} \geq 2.1\%$. The alternative hypothesis was : $\pi_{rPA} - \pi_{SK} < 2.1\%$. The use of the 2.1% value was based on a meta-analysis. As described in the original clinical protocol, the meta-analysis performed by the Fibrinolytic Therapy Trialist Collaborative Group demonstrated that thrombolytics provided a mortality benefit over placebo controls with the lower boundary for the thrombolytic - placebo mortality benefit being 2.1%.[5] The hypothesis testing incorporated in the statistical analytical section of the original INJECT protocol did not directly address the "50% rule." However, in post-hoc analytical testing the sponsor does apply the "50% rule" to the INJECT mortality results and uses confidence intervals.

The efficacy evaluation for the indication of "lysis of thrombi obstructing coronary arteries, the improvement of ventricular function following AMI and the reduction of the incidence of congestive heart failure following AMI" must also be indirectly based on historical controls. There is little precedent for evaluating these secondary indications in a comparative trial and no specific directions for evaluating these secondary indications /endpoints were proposed by either the FDA or the sponsor prior to initiation of the rPA controlled clinical trials. The most recently licensed thrombolytics (tPA and anistreplase) had two of these "secondary" indications (incidence of congestive heart failure and ventricular function) demonstrated in placebo -controlled trials. The efficacy endpoint of coronary thrombolysis was demonstrated in a placebo controlled trial for tPA, but in a subjective comparison to SK for anistreplase.

1.3 Materials Reviewed:

The materials reviewed included: original clinical protocols, blank case report forms, study reports, and original IND materials for all the clinical studies. The completed case report forms from 59 selected patients were reviewed for INJECT. SAS data sets were reviewed with Dr. G. Gupta (PLA committee statistician).

1.4 Indication:

The sponsor claims reteplase "is indicated for use in the management of AMI in adults for the lysis of thrombi obstructing coronary arteries, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI."

•Reviewer's note: These are largely the same licensed indications for streptokinase, tissue plasminogen activator, and anistreplase.

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4. Makuch, R, Johnson, M. Issues in planning and interpreting active control equivalence studies. J Clin Epidemiol 1989;42:503-511.

5. FTT Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343:311-322.

1.5 Product and Manufacturing:

Reteplase (rPA) is a non-glycosylated deletion variant of tissue plasminogen activator (tPA). produced in *E. coli.* rPA differs from tPA in that rPA lacks three domains ( ) and glycosylation. Because it retains the kringle 2 domain, some fibrin specificity is maintained. However, *in vitro* studies demonstrate that rPA maintains only 30% of the fibrin specificity of tPA. Additionally, clinical studies suggest that the fibrin specificity for rPA is not equivalent to that of tPA (equipotent doses of rPA and tPA result in much greater lowering of the fibrinogen level by rPA). The deletions in rPA also result in a longer half life. While the half life for tPA is only four minutes, that for rPA is approximately 13-16 minutes (based on the measurement of thrombolytic activity). Consequently, the development of the product has been designed to allow for dosing as a bolus method. The proposed adult dose is 10 MU (1 megaunit = 1 U in a Reteplase-specific clot lysis assay) IV, initially, followed in 30 minutes by a repeat IVdose (bolus injection over two minutes). The sponsor has performed a series of studies which attest to the use of rPA in acute myocardial infarction. The pivotal study is a comparison of rPA to SK. The initial studies with rPA were performed under ——— which was filed on July 1, 1991. The product is manufactured by Boehringer Mannheim GmbH in Germany and is to be distributed in the USA by Boehringer Mannheim Corporation (Indianapolis, IN). The final product formulation is a sterile, white, lyophilized powder for intravenous bolus injection after reconstitution with 10 ml sterile water. The quantitative composition of each vial of the lyophilized product is:

10 U Vial	
Reteplase	17.4 mg
L-arginine	871.0 mg
phosphoric acid	286.6 mg
polysorbate	201.0 mg

Reteplase is not currently licensed for marketing in any country.

Because of patent requirements, the plasmid promoter used in manufacturing was changed during the phase 3 trials. The promoter was changed from a ( )

•Reviewer's comment: The promoter was changed from for patent conflict reasons, not scientific ones. The sponsor has documented that material produced using each promoter is equivalent biochemically and pharmacokinetically (in humans) and, in general, there is no reason to expect a change in the product.

1.6 Clinical Studies:

The sponsor has performed a series of studies which assess the safety and efficacy of the use of rPA in patients with acute myocardial infarctions (Table 1). The sponsor performed phase 1 studies in healthy subjects. Phase 2 and phase 3 studies were performed in patients with AMI (Table 5). The phase 3 controlled clinical studies were comparative studies. No phase 3 placebo-controlled studies were performed. Overall, this data base includes a total of 7208 patients, of which 3850 received rPA. Reteplase was administered to a total of 3805 patients with AMI and to 45 healthy volunteers. The doses of rPA used in these studies involved single injections in doses ranging from 0.1125 MU to 15 MU or, two injections of either 10 + 5 MU or 10 + 10 MU.

Table 1. Clinical trials

Trial	Reference Title	Dates	Patients rPA/other/total	Phase	Location/Sites
MF 7076	none	4/1990-5/1990	18 / 0 / 18	1	Germany /1
MF 7082	none	8/1990	7 / 7 /7*	1	Germany /1
M 2	none	9/1991-12/1991	20 / 4 / 24	1	Japan /1
MF 4207	GRECO	10/1990-4/1991	142 / 0 / 142	2	Germany /16
MF 4267	GRECO-DB	5/1991-11/1991	52 / 0 / 52	2	Germany /13
MF 4292	none	12/1992-4/1994	25 / 0 / 25	2	Germany /1
MF 4255	RAPID-1	8/1991-5/1994	452 / 154 / 606	3	USA/Europe/ 38
MF 4401	RAPID-2	11/1993-10/1994	169 /155 / 324	3	USA/Europe/ 26
MF 4344	INJECT	8/1993-10/1994	3004 / 3006 / 6010	3	Europe/ 208

*cross-over design

1.6.1 Phase 1 Studies: The phase 1 studies (protocols 7076, 7082 and M2) were all single center studies that provided the initial safety and pharmacokinetic evaluations of reteplase. Study 7076 was an open-label, noncontrolled, nonrandomized, dose-escalation study in which patients received a single IV injection of rPA. The doses ranged from 0.1125 MU to 5.5 MU. Study 7082 was a single-blind, placebo-controlled, randomized, cross-over study in which patients received an IV injection of a placebo (vehicle) and 6 MU rPA. These first two studies were performed in Germany. The study designated as M2 was a placebo-controlled, single-blind, Japanese study in which patients were randomized to receive one of four IV rPA bolus doses, with doses ranging from 0.5 MU to 4 MU, or a placebo. These studies involved a total of 49 subjects, of which 45 received rPA.

1.6.2 Phase 2 Studies: The three phase 2 studies were all open-label, noncontrolled studies performed in patients with AMI. These studies were designed to provide the initial coronary arteriographic evaluations of thrombolysis. The studies designated as GRECO MF (protocol 4207) and GRECO DB (protocol 4267) were both nonrandomized, multicenter, dose-finding studies. Patients in GRECO MF were treated with one of two rPA doses (10 MU or 15 MU), given as a single IV bolus injection. GRECO DB studied a single dose of rPA delivered as two IV bolus injections (10 MU, followed 30 minutes later by 5 MU--a "double bolus"). In study 4292 patients were randomized to one of three rPA doses (15 MU given as a single IV bolus injection, or 10 MU followed in 30 minutes by 5 MU, or 10 MU followed in 30 minutes by another 10 MU injection). These studies involved a total of 219 patients and were performed in Germany.

1.6.3 Phase 3 Studies: There were three phase 3 studies. All three studies were multicenter, multinational, controlled clinical trials. Two of the studies (RAPID-1 and RAPID-2) included patients enrolled in the USA, while the pivotal trial was conducted in Europe. The first study was called RAPID-1 (protocol 4255) and was conducted in the USA, Germany, Austria and the UK. This study was a four arm study in which rPA was compared to (standard dose) tPA. Overall, 606 patients were randomized to one of four dose arms--15 MU single bolus rPA, 10 + 5 MU double bolus rPA, 10 + 10 MU double bolus rPA or 100 mg tPA (standard infusion, over 3 hrs). This study is viewed, by the sponsor, as the primary dose finding study. The primary endpoint for this study was 90 minute arteriographic patency. All three phase 3 studies required the adjunctive treatment of patients with aspirin and IV heparin.

The pivotal study was called INJECT (protocol 4344). This study compared rPA (10 + 10 MU, double bolus) to streptokinase (SK, 1.5 million units over 1 hour). There were 6,010 patients studied, with 2,279 being from the UK and 1,910 from Germany and the remainder from other European countries. 35 day mortality was the primary clinical endpoint.

The study called RAPID-2 (protocol 4401) compared rPA (10 + 10 MU, double bolus) to accelerated -dose tPA (100 mg, given over 90 minutes). A total of 324 patients were studied in RAPID-2. 247 of the patients were in the USA and the remainder were in Germany.

1.7 Overview of the Results from the Clinical Studies:

The phase 1 and phase 2 studies demonstrated that rPA has linear pharmacokinetics over the dose range of 0.1125 to 20 MU and exhibits a half-life of approximately 14 minutes. These studies also demonstrated that rPA administration (at doses below 15 MU) resulted in a dose-related decrease in the blood fibrinogen, plasminogen and α-2 antiplasmin concentrations, suggesting that the most likely complications of rPA administration were to be related to hemorrhage. Of the 268 patients studied exposed to rPA in the phase 1 and 2 studies, there were two strokes (patients treated with 15 MU rPA) and five deaths (four patients treated with 15 MU rPA and one patient treated with 10 MU rPA). One of the strokes was due to an intracerebral hemorrhage. The results of the phase 1 and 2 studies will not be reviewed in detail.

Unlike the findings from the phase 1 and 2 studies, the higher doses (15 MU, 10 + 5 MU, or 10 + 10 MU) studied in the first phase 3 study (RAPID-1) did not demonstrate a dose-related decrease in blood concentrations of fibrinogen, plasminogen or α-2 antiplasmin. In RAPID-1, the mean trough value for blood fibrinogen was approximately 26% of baseline following rPA administration. The patients treated in RAPID-1 with rPA had a greater decrease in their blood fibrinogen concentrations than patients treated with a standard dose of tPA, suggesting that the fibrin-specificity for rPA was less than that for tPA (findings consistent with the in vitro data). RAPID-1 also suggested that the 10 + 10 MU rPA dose produced higher coronary artery patency and TIMI 3 flow rates than other (15 MU or 10 + 5 MU) rPA doses. This dose (10 + 10 MU rPA) was used in the two subsequent phase 3 studies.

The results of all three phase 3 studies are summarized in Tables 2 and 3. There were two phase 3 studies that had coronary artery patency as their primary endpoint (RAPID-1 and RAPID-2). These studies demonstrated that the coronary thrombolytic effects of rPA were at least comparable to those of tPA (Table 3). The effects of rPA upon ventricular function also appeared comparable to those of tPA.

The effect of rPA upon the mortality rate of patients suffering myocardial infarctions was the primary endpoint in the largest clinical trial, INJECT. INJECT demonstrated that the mortality rate (9.0%) of patients treated with rPA (10 + 10 MU) was no worse than the mortality rate (9.5%) of patients treated with streptokinase (1.5 million units). INJECT demonstrated that the incidence of congestive heart failure was lower among the patients treated with rPA than the patients treated with SK. The incidence of stroke was not statistically different between the two study arms. The other adverse events were similar and of comparable incidences between the study arms. The subsequent portion of this review will detail the results of the phase 3 studies.

Reviewer's comment: Unless noted otherwise, all proportions in the tables in this review are compared using a Chi-square test (P).*

Table 2. Number (%) of patients with selected outcomes in phase 3 clinical trials

Clinical Outcome‡ Number of patients (%)	RAPID-1				RAPID-2		INJECT		Total
	rPA 10 + 10 MU	rPA 10 + 5 MU	rPA 15 MU	tPA 100 mg (3 hr)	rPA 10 + 10 MU	tPA 100 mg (1.5 hr)	rPA 10 + 10 MU	SK 1.5 Mi U	
Enrolled (n)	154	152	146	154	169	155	3004	3006	6940
Deaths	3 (2%)	11 (7.2%)	6 (4.1%)	6 (3.9%)	7 (4.1%)	13 (8.4%)	270 (9.0%)	285 (9.5%)	601 (8.7%)
With strokes	0 0	0 0	1 (0.7%)	6 (3.9%)	3 (1.8%)	4 (2.6%)	42 (1.4%)	33 (1.1%)	89 (1.3%)
hemorrhagic	0 0	0 0	1 (0.7%)	4 (2.6%)	2 (1.2%)	3 (1.9%)	23 (0.8%)	12 (0.4%)	45 (0.6%)
nonhemorrhagic	0 0	0 0	0 0	2 (1.3%)	1 (0.6%)	0 0	15 (0.5%)	10 (0.3%)	28 (0.4%)
uncertain	0 0	0 0	0 0	0 0	0 0	1 (0.6%)	4 (0.1%)	11 (0.4%)	16 (0.2%)
With bleeds requiring transfusion	21 (13.6%)	11 (7.2%)	10 (6.9%)	14 (9.1%)	21 (12.4%)	15 (9.7%)	26 (0.9%)	35 (1.2%)	153 (2.2%)
With any bleed	75 (48.7%)	64 (42.1%)	56 (38.4%)	76 (49.4%)	76 (45%)	73 (47.1%)	451 (15%)	460 (15.3%)	1331 (19.2%)
With CHF	9 (5.8%)	12 (7.9)	5 (3.4%)	9 (5.8%)	16 (9.5%)	19 (12.3%)	754 (25.1%)	860 (28.6%)	1684 (24.3%)
With recurrent MI	4 (2.6%)	7 (4.6%)	9 (6.2%)	7 (4.5%)	8 (4.7%)	7 (4.5%)	196 (6.5%)	197 (6.6%)	435 (6.3%)

‡at 30-35 days

Table 3. Selected coronary arteriographic results in phase 3 clinical trials

Outcome	RAPID-1				RAPID-2	
	rPA 10 + 10 MU	rPA 10 + 5 MU	rPA 15 MU	tPA (100 mg, 3 hr)	rPA 10 + 10 MU	tPA (100 mg, 1.5 hr)
% (95% CI) of Patients with patency (TIMI 2 or 3) at 90 minutes	85.2% (79-91)	66.7% (59-75)	62.8% (55-71)	77.2% (70-84)	83.4% (78-89)	73.3% (66-81)
% (95% CI) of Patients with TIMI 3 at 90 minutes	62.7% (55-71)	45.7% (37-54)	40.9% (33-49)	49.0% (41-57)	59.9% (52-68)	45.2% (37-53)
Ejection fraction (early)*						
%, mean ± SE	49.8 ± 1.4	52.4 ± 1.4	50.8 ± 1.6	51.6 ± 1.4	52.3 ± 1.0	52.8 ± 1.0
median	50.4	54.0	52.1	53.5	54.0	55.2
Ejection fraction (late)**						
%, mean ± SE	52.9 ± 1.3	53.2 ± 1.3	49.6 ± 1.4	49.0 ± 1.3	52.0 ± 1.2	53.8 ± 1.0
median	54.3	54.3	52.5	51.4	54.4	54.2
Reg wall motion (early)*						
mean ± SE	-2.55 ± 0.14	-2.53 ± 0.13	-2.86 ± 0.13	-2.65 ± 0.14	-2.53 ± 0.08	-2.76 ± 0.10
median	-2.87	-2.66	-3.14	-2.94	-2.69	-2.85
Reg wall motion (late)**						
mean ± SE	-2.19 ± 0.12	-2.35 ± 0.12	-2.54 ± 0.12	-2.61 ± 0.13	-2.28 ± 0.11	-2.29 ± 0.11
median	-2.34	-2.41	-2.70	-2.85	-2.31	-2.29

*near the 90 minute time point
**at follow-up (generally 5-7 days)

Reg = regional wall motion expressed in units of standard deviation from the mean normal value (more negative numbers indicate greater cardiac dysfunction)

2.0 Detailed Review of INJECT (International Joint Efficacy Comparison of Thrombolytics) Design:

2.1 Overview:

INJECT was entitled: "A randomized, double-blind, multinational multicenter trial to compare the effects of reteplase (10 MU + 10 MU IV, double bolus) with that of standard therapy with streptokinase (1.5 MU IV infusion) on 35 day mortality in patients with acute myocardial infarction."
INJECT compared the efficacy and safety of Reteplase with streptokinase in patients with acute myocardial infarctions.

Two organizations were primarily responsible for daily management of the trial:
-Boehringer Mannheim GmbH (BM)
provided day to day responsibility for the management of the study
an independent data center under contract to BM; provided data management and logistical support.

The responsibility for management of the trial was divided among four committees:

1. Executive committee:3 university professors and a nonvoting BM representative
2. Steering committee:
   consisting of an executive committee plus national coordinators
3. Safety Committee:
   -conducted regular reviews of both efficacy and safety data
   -consisted of a chairman (unblinded, nonBM) and two other (non BM) members
   -the chairman received weekly safety reports, which included recruitment to each group and the number of deaths to date by treatment. Event frequencies for strokes, reinfarction, serious bleeds and other serious adverse events (AE) were also provided. These summaries were prepared, unblinded, by a statistician within the [redacted] and were disclosed only to the chairman.
   -at four-weekly intervals, a similar report was sent to the regular members of the safety committee with the treatments identified as A and B.
   -met within 30 days of the recruitment of 1000 patients, and then was to meet at three-monthly intervals. The committee was also requested to meet to consider the continuing progress of the study if either observed in-hospital mortality rates for the two treatment groups were different to the extent:
      -of at least 5% when total recruitment was between 1000 and 2000 patients
      -of at least 4% when total recruitment was greater than 2000 patients
      or
      -a difference of at least 2% was observed in the in-hospital stroke rates when total recruitment was between 1000 and 2000 patients
      -a difference of at least 1.5% was observed in the in-hospital stroke rates when total recruitment was greater than 2000 patients.

•As the trial progressed, all 3 members of the safety committee had access to unblinded results. Since there was no affiliation of the safety committee members to BM or the investigators, it is unlikely that the safety committee oversight might bias the trial performance or results. Only the safety committee was to have access to patient data.

4. Technical Committee:
   consisted of at [redacted] a Center statistician and coordinator, a University administrative coordinator, a BM project coordinator, a BM statistician, and a BM clinical research associate.

The first patient was entered into the study on August 24, 1993 and recruitment was terminated on September 20, 1994. Six month follow-up of all patients was completed during April, 1995.

2.2 Investigators/Sites/Monitoring:

INJECT was designed to be a multinational, multicenter study, conducted solely in Europe. The protocol stated that it was anticipated that each center would enroll approximately 40 patients. A contract research organization, [redacted] monitored at least 10% of all patients enrolled at every site in the trial. An independent audit of selected sites and the [redacted] Center was performed by the Quality Assurance Department of Boehringer Mannheim. The FDA inspected selected sites for protocol adherence and compliance with case report record maintenance.

•Reviewer's comment: The statistical powering of the sample size, as stated in the original protocol required that at least 5880 patients be evaluable. Excluding the 71 patients who did not receive either trial medication left 5939 patients who did receive medication, thereby meeting the prestated enrollment goal.

2.3 IRB/CRF:

Informed consent was obtained and documented for all patients in the study. All investigational sites had the protocol approved by their local ethics review board.

2.4 Design:

Multinational, multicenter, double-blind, parallel group study randomizing patients to receive either SK or rPA. In certain places within the original clinical protocol references to the trial as an equivalency trial are made. However, the powering of the trial was based on a "not worse than" approach. The double-blind design was achieved using a double-dummy regimen in which patients assigned Reteplase also received a placebo infusion over one hour commenced directly after the first bolus. Patients assigned streptokinase also received 2 placebo bolus injections, one immediately prior to the start of the infusion and the second 30 minutes later

There were two amendments to the original clinical protocol:

-Amendment number 1 (August 2, 1993) required the collection of cardiovascular endpoints occurring between discharge/transfer and 35 days after thrombolysis.

-Amendment number 2 (July 7, 1994) stated that: where the 35 day status of patients is unknown, but the 30 day follow-up status is known, the status on the day of assessment will be used.

•Reviewer's comment: The term "35 day mortality" thus included some patients with follow up information obtained at ranges of 30 to 35 days following thrombolysis. As displayed in the results section, this five day range for 35 day mortality is unlikely to have clinical significance, since the mortality estimates (Kaplan-Meier curves) had largely plateaued by this time.

2.5 Objectives:

As stated in the protocol, the primary objective of the study was to demonstrate that rPA was as effective as SK in limiting 35 day mortality. The statistical analysis section of the protocol stated that the objective of the trial was to demonstrate the equivalence of, or the superiority of, rPA to standard therapy. The protocol listed secondary objectives as "net clinical benefit"--the proportion of patients who are not dead at 6 months nor disabled as a consequence of an in-hospital stroke.

2.6 Inclusion Criteria:

-18 years of age and older (no upper age limit)
-chest pain of at least 30 min and consistent with coronary ischemia
-persistent ST-segment elevation of $\geq$ 0.1 mV in 2 of 3 inferior leads, or $\geq$ 0.1 mV in leads I and aVL or $\geq$ 0.2 mV in 2 contiguous precordial leads or bundle branch block
-sufficient time to ensure that thrombolysis could be initiated within 12 hours of the onset of chest pain

2.7 Exclusion Criteria:

-Cerebrovascular risks: prior cerebrovascular event (CVA) or transient ischemic attack (TIA); intracranial neoplasm, A-V malformation or aneurysm
-Bleeding risks: known proliferative diabetic retinopathy, known hemorrhagic diathesis, any clinically

relevant recording of SBP ≥ 200 mm Hg during the presenting illness prior to randomization, or uncontrolled hypertension at any time prior to entry (SBP >200 mm Hg or DBP >100 mm Hg on several measurements) which does not respond rapidly to treatment; concomitant use of oral anticoagulants; or any of the following within the prior two weeks--prolonged or vigorous cardiac massage, puncture of noncompressive vessel, coronary angioplasty (PTCA); or any of the following within the prior three months-- organ biopsy or major surgery (intracranial, intraspinal, intraocular); active or potential internal bleeding (peptic ulcer, esophageal varices or any major trauma).

-Other: pregnant/nursing; administration of any investigational drug within 30 days prior to enrollment in this study; any other disease which, in the judgement of the investigator, would place a patient at undue risk or confound the results of the study (malignancy, AV malformations, endocarditis, colitis); any other contraindication specified in the package insert of streptokinase; treatment with streptokinase or anistreplase in the prior 12 months; previous enrollment in this study.

2.8 Dose:

Patients received either two 10 MU boluses of rPA, separated by 30 minutes, and an infusion of placebo or two boluses of placebo and a 1.5 million U infusion of SK. All patients were to receive IV heparin, 5,000 U bolus given immediately prior to the first bolus of trial medication, followed by 1,000 U/hr from the completion of the trial infusion. The heparin infusion was to be continued for at least 24 hours. Heparin was to be adjusted to maintain an APTT of at least twice the control. Heparin infusion rates could be adjusted upward to achieve this level. Twelve hours or more after thrombolysis heparin infusion rates could be reduced if the aPTT levels were too high.

•Reviewer's comment: This heparin regimen duplicates the regimen commonly utilized clinically, as well as that utilized for tPA and one of the SK arms in GUSTO-1.

Therapy with aspirin (250-350 mg day 0; 75-150 mg/day thereafter) was recommended from day 0 to hospital discharge---but was not required.

Reteplase was supplied as a lyophilized product, which was reconstituted with 10 ml sterile water. The placebo companion to reteplase was also lyophilized. Placebos could not be distinguished from the study agents. Randomization was regulated centrally. A predetermined randomization sequence was constructed using the method of randomized permuted blocks with a block size of six. Each investigational site was supplied with one or more packs of twelve treatment kits. Within each pack, the kits were numbered consecutively, but the order in which the kits were to be used was determined by a further permutation of the numbers within a pack which was held by the investigational site's designated randomization center. Once a patient had been identified as eligible, the investigational site placed a telephone call to their designated randomization center. The investigational site was instructed which kit to use. Daily reports of recruitment made by the randomization centers were supplied to the [redacted]. Confirmation that the patient had received the allocated treatment was indicated by attaching a sticky label supplied with the kit and bearing the kit number to the case record form. 24 hr randomization services were supplied by the:

[redacted] (UK, Sweden, Finland, Lithuania)
[redacted] (Germany, Austria)
[redacted] (Poland)
[redacted] (Hungary)
-BM Therapeutics, Barcelona (Spain).

Physicians were permitted to request that the treatment be revealed for individual patients in the case of medical emergency. A copy of the treatment codes was held by each randomization center. Requests for code breaks were made by telephone to a randomization center, who revealed the code to the caller and made a record of the reason given for the code break. If additional thrombolysis was needed, alteplase or urokinase were to be used.

There were no restrictions on concomitant medications, therapies or additional thrombolytics. Surgical intervention or PTCA were permitted.

2.9 Evaluations:

1. Clinical laboratory:
   - -hemoglobin prior to thrombolytic dosing and 48 hours later
   - -if the optional troponin T substudy was conducted, blood was drawn prior to thrombolysis, and at 2, 10, 24 and 72 hours after the initiation of thrombolysis
   - -Serum CK was obtained as often as was clinically indicated and the highest value documented
   - -Serum fibrinogen was recommended to be measured at 4 hours after thrombolytic dosing
   - -Serum antibody was measured at baseline, before discharge (if the patient is hospitalized for more than 10 days) or between days 35 and 50, if the patient's hospital stay is less than 10 days
2. EKG: at baseline and as clinically required
3. Clinical monitoring:
   - -VS at baseline
   - -adverse events (AE) throughout the 35 days following thrombolytic dosing
4. Follow-up information
   - -mortality status at 35 days and 6 months
   - -functional assessment at 6 months, for patients suffering a stroke
   - -cardiovascular endpoint outcomes throughout the 35 days following thrombolytic dosing (angina, congestive heart failure, arrhythmia, CABG, PTCA, stroke)

•Reviewer's comment: The functional outcome assessment for patients who had suffered a stroke was limited to a determination by the investigator. Patients were assigned to one of 4 possible stroke outcomes: no sequelae; minor sequelae, but fully independent; significant limitation of activity, but some degree of independence; unable to live or work independently. The protocol did not supply additional information relating to the method of functional assessment and no submitted materials demonstrate that there was an effort to maintain consistency of the functional assessment across the investigational sites or from patient to patient at each investigational site. Hence, the functional outcome assessment should be regarded as relatively subjective and potentially variable from site to site.

The troponin T substudy was an exploratory substudy performed at a limited number of sites and appears irrelevant to the main clinical trial. The details of the troponin T were not submitted in the license application.

2.10 Endpoints:

As stated in the original protocol, the primary endpoint of the study was all cause mortality at 35 days. The secondary endpoint was "net clinical benefit." Other variables of interest, as stated in the protocol, included:

- -in-hospital mortality
- -mortality at 6 months
- -in-hospital incidence of stroke
- -in-hospital frequency of intervention therapy
- -in-hospital incidence of reinfarction and recurrent ischemia
- -in-hospital incidence of congestive heart failure
- -in-hospital incidence of non-cerebral bleedings
- -formation of antibodies against rPA

2.11 Adverse Event Classification:

Adverse events (AE) were classified in several ways. Each AE was to queried with respect to three categories:

- -as either serious or nonserious
- -as alarming
- -as "of special interest."

"Immediate notification" CRF pages were available for "alarming AE or AE of special interest." If serious AE was also classified as alarming or of special interest, only the immediate notification forms were to be

completed. Serious AE, which were not alarming or of special interest, were detailed on a serious AE form. The AE classified as "alarming" or "of special interest" had to be reported to the safety coordinator within 24 hrs of the event. All other AE were reported either at hospital discharge or 35 days. An AE was described as "alarming" if all of the following occurred:

-the event was fatal or life-threatening
-the event was unexpected
-there was a reasonable suspicion of a causal relationship to the trial medication.

An AE was described as "AE of special interest" if:

-the event was a bleed requiring transfusion
-the event was a cerebrovascular event
-the event resulted in death.

The decision to classify an AE as serious, alarming or of special interest was made by the site investigator. Causality was not assessed by the center. Causality for all AE of special interest was assessed independently by the BM safety officer and by the Trial International Coordinator (who was independent of the sponsor). Causality for all other serious AE was assessed by the Trial International Coordinator alone.

Cerebrovascular events were further defined in the protocol as:

-a TIA was defined as a complete recovery of neurological deficit within 24 hrs; prolonged reversible ischemic neurological deficit (PRIND) was defined as a neurological deficit of more than 24 hrs duration, which was reversed in a short time leading to complete recovery;
-strokes were categorized according to whether they were hemorrhagic or nonhemorrhagic on the basis of CT, when possible. However, a diagnosis on clinical grounds was acceptable if no CT scan or post mortem evidence was available. The classification of all cerebrovascular events was made by the investigator at the center (no central review).

Bleeds were further categorized as:

-to site: puncture site, retroperitoneal , gastro-intestinal, genito-urinary or hemoglobin drop greater than 3 gm/dl with an unidentified site
-fatal/or required transfusion
-life-threatening/prolonged hospitalization.

•Reviewer's comment: AE occurring after 35 days were not recorded. The degree of bleeding was not prospectively defined using a classification system (such as number of units transfused). However, bleeding of sufficient degree to require transfusion was prospectively stated in the protocol to be distinguished from lesser bleeding. The protocol did not define "stroke."

2.12 Planned Statistical Analysis:

As stated in the clinical protocol, the powering of the study and the efficacy analysis were to use a "not worse than" approach where the expected mortality rate of SK is 8%. A meta-analysis (later published by the Fibrinolytic Therapy Trialists' Collaborative Group; Lancet 1994;343:311-22) provided an estimate for the absolute mortality reduction of thrombolysis compared with placebo of 2.6% (which had a 95% CI lower bound of 2.1 percentage points). The stated primary null hypothesis was : the mortality rate for rPA - the mortality rate for SK is greater than or equal to 2.1%. The sample size was then calculated for an alpha error of 5% and a beta error of 10%. The primary endpoint would then be calculated by subtracting the two mortality rates. If rPA had a mortality rate equal to or greater than SK by 2.1%, then the null hypothesis could not be rejected and rPA failed. If the rPA - SK mortality rate was less than 2.1%, then it was to be concluded that rPA was no worse than SK, with respect to mortality benefit. Subsequently, a test of superiority , "in the confirmative sense" was to be performed (if the primary null hypothesis were rejected). In this secondary analysis, the primary hypothesis was to be that the rPA mortality - SK mortality was

greater than or equal to 0. Rejection of this null hypothesis would suggest that rPA was superior to SK.

No statistical plan for AE analysis was stated in the clinical protocol.

No interim analyses of efficacy were planned or performed.

3.0 INJECT Trial Performance Data:

3.1 Recruitment:

The first patient was enrolled on August 24, 1993. Recruitment was terminated on September 20, 1994 and six month follow-up of all patients was completed during April, 1995. A total of 6010 patients were enrolled in the trial, at 208 centers in 9 countries.

Table 4. Recruitment by Country

Country	Number of Sites (%)	Number of Patients Enrolled, n (%)			Patients Per Site, n
		Total	rPA	SK	
UK	56 (27%)	2280 (38%)	1136(38%)	1144 (38%)	41
Germany	95 (46%)	1909 (32%)	958 (32%)	951 (32%)	20
Poland	25 (12%)	1098 (18%)	549 (18%)	549 (18%)	44
Sweden	6 (3%)	292 (5%)	145 (5%)	147 (5%)	49
Austria	3 (1%)	28 (0.5%)	12 (<1%)	16 (<1%)	9
Finland	6 (3%)	129 (2%)	65 (2%)	64 (2%)	22
Hungary	9 (4%)	175 (3%)	91 (3%)	84 (3%)	19
Lithuania	2 (1%)	46 (0.5%)	23 (1%)	23 (1%)	23
Spain	6 (3%)	53 (1%)	25 (1%)	28 (1%)	9
Total	208 (100%)	6010 (100%)	3004 (100%)	3006 (100%)	29

•Reviewer's comment: Nearly 90% of the enrolled patients (88%) were in the UK, Germany or Poland. The median center enrollment was 11-20 patients (60 of the 208 centers). Only four centers enrolled more than 100 patients (centers in the UK).

3.2 Randomization Errors:

There were 3 patients who were assigned randomization numbers incorrectly. One patient (number [redacted] was withdrawn from the study by the investigational site (without receiving INJECT medications) and no information is available regarding this patient. One patient was assigned a randomization number, but had already been enrolled in the study and had received SK at an earlier date. (This patient received SK again, without incident). The third patient was to be enrolled in another rPA study, but was inadvertently assigned an INJECT randomization number, but received no INJECT medication. These 3 patients are not included among the 6010 enrolled patient population.

•Reviewer's comment: Considering the size of the trial this is not an unreasonable management of the randomization errors.

3.3 Codebreaks:

Requests for a codebreak were received for a total of 53 patients. Most of the codebreaks were related to the site investigator's request to evaluate an AE (such as stroke, bleeding, hypotension or death). Most of the code breaks were from sites in the UK (23) or Germany (21). Following the first several

months of patient enrollment, investigators were informed to only use codebreaks when the information was necessary for the patient's future management.

•Reviewer's comment: Less than 1% of the enrolled patients had codebreaks.

3.4 Data Completeness:

At the time of data analysis (January, 1995) there were 6 patients lacking in-hospital data and 24 patients (0.4%) lacking 35 day outcome data. Six month outcome data were missing for 148 patients (2.5%).

Table 5. Data Completeness

	rPA		SK		Total	
	n	%	n	%	n	%
Enrollment	3004	100	3006	100	6010	100
In-hospital data available	3001	99.9	3003	99.9	6004	99.9
In-hospital data not available	3	0.1	3	0.1	6	0.1
35 day outcome available	2994	99.7%	2992	99.5%	5986	99.6%
35 day outcome not available	10	0.3	14	0.5	24	0.4
180 day outcome available	2925	97.3	2937	97.7	5862	97.5
180 day outcome not available	79	2.6	69	2.3	148	2.5

•Reviewer's comment: 12 of the 24 patients with missing 35 day outcome data were enrolled in the UK, the other patients were enrolled in Germany, Poland, Austria and Hungary. 10 of these 24 patients received rPA and 14 received SK. These 24 patients are not included in the primary efficacy analysis.

3.5 Protocol Violations: There were a total of 121 patients that had at least one protocol violation of enrollment inclusion or exclusion criteria. The most common violations are detailed below:

Table 6. Patients with Protocol violations

Number randomized	rPA		SK		Total	
	n = 3004	%	n = 3006	%	n = 6010	%
At least one	64	2.1	57	1.9	121	2
Prior CVA	16	0.5	18	0.6	34	0.6
Lacked EKG criteria	13	0.4	10	0.3	23	0.4
Lacked chest pain criteria	8	0.3	8	0.3	16	0.3
Lacked BP criteria	5	0.2	5	0.2	10	0.2
Active internal bleeding or trauma	2	0.1	5	0.2	7	0.1
Other diseases requiring exclusion	4	0.1	2	0.1	6	0.1
Treatment with SK or anistreplase in prior 12 months	4	0.1	2	0.1	6	0.1
Other*	10	0.3	11	0.4	21	0.3

*known hemorrhagic diathesis, prior organ biopsy, other diseases increasing risk

•Reviewer's comment: The patients enrolled in violation of inclusion or exclusion criteria were balanced

between the two treatment arms.

3.6 Patient Population for Analyses: There were 3 patients among the 6010 enrolled patients who had no data available for analysis. There were 71 patients who did not receive any trial medication and 126 patients who received incomplete courses of the trial medications.

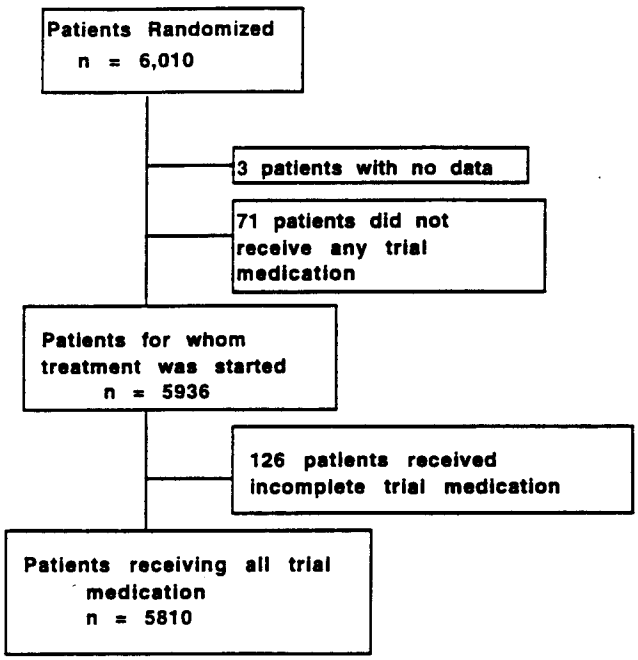


Figure 1. INJECT PATIENT POPULATIONS

•Reviewer's comment: The sponsor performed analyses using all patients (6010) and patients for whom treatment was started (5936). All analyses in this review will use the total number of enrolled patients (6010) unless noted otherwise. The number of patients who did not receive any trial medication was fairly evenly divided (rPA = 38 patients, SK = 33 patients) between the trial arms, as was the number of patients who received incomplete trial medication (rPA= 61 patients, SK = 65 patients). Of the 5936 patients for whom treatment was started, rPA= 2965 patients and SK = 2971 patients.

4.0 Results

4.1 Patient Baseline Characteristics:

Table 7. Distribution of patients

Variable	Category	rPA	SK	P*
Sex	Male	2155 (72%)	2190 (73%)	0.33
	Female	846	813	
Race	Caucasian	2968 (99%)	2977 (99%)	0.43
	Other	32	26	
Weight (kg)	n =	2671	2650	0.67
	mean ± SD	76.5 ± 13.3	76.7 ± 13.4	
Age (years)	n=	2997	2650	0.71
	mean ± SD	62.3 ± 11.5	62.5 ± 11.7	

*Chi-square for proportions and t test for continuous variables

4.1.1Age: Patients entered into the trial ranged in age from 20 to 96 years, with a mean of 62 ± 12 years (SD). Subgrouping the patients by age (< 50, -65, -75, >75) showed that patients were evenly divided between the two treatment arms. There were 1710 patients (28%) aged 65 to 75 years and there were 712 (12%) patients aged greater than 75 years.

4.1.2 Sex: Most (72%) of the patients were male and were evenly divided between the two treatment arms (rPA = 2158 male patients, SK = 2191 male patients).

4.1.3 Weight: The weights of the enrolled patients varied between 38 kg and 202 kg with a mean of 77 ±13 (SD) kg. 18% (1061) of the patients had a weight equal to or less than 65 kg. 30% (1811) of the patients had a weight greater than 80 kg. 11% (667) patients weighed more than 90 kg. 689 patients (11%) did not have weights recorded.

4.1.4 Smoking History: 66% of the enrolled patients (3996 patients) were either cigarette smokers or had a history of smoking. The arms were evenly balanced (rPA = 2013, SK = 1983).

4.1.5 Ethnicity: Almost all enrolled patients were caucasian (5945 patients, 99%). Only 2 African-origin patients were enrolled in each trial arm and only 29 patients were of Asian origin.

•Reviewer's comment: These demographics (age and sex) are similar to those in the published report of GUSTO-1, except the incidence of smoking was lower in GUSTO (43%), ethnicity was not reported for GUSTO-1, and weights were not reported for GUSTO.

4.2 Patient Comparability between the Trial Arms:

4.2.1 Time to Treatment: The median time from onset of symptoms to treatment with thrombolytics was 3 hours 25 minutes and 4 hours 8 minutes, mean. The mean times were comparable between the two arms (rPA = 4.2 ± 2.8 hours, SK = 4.1 ± 2.4 hours). 80% of patients for whom treatment was started, received treatment within six hours of symptom onset (rPA =2358, SK = 2407, with 27 of the 5936 patients for whom treatment was started missing this information).

4.2.2 Historical Factors: The other historical factors describing the enrolled patients are shown below in Tables 8 and 9.

Table 8. Comparability of treatment groups

Variable	rPA (n = 3004)	SK (n = 3006)	Total (n = 6010)	P-value*
Prior MI	434 (14%)	441 (15%)	875 (15%)	0.25
Missing or unknown MI history	58 (2%)	43 (1%)	101 (2%)	
Prior use of SK or tPA	61 (2%)	67 (2%)	128 (2%)	0.20
Missing or unknown prior use of SK or tPA	53 (2%)	28 (1%)	81 (1%)	
History of diabetes mellitus	345 (11%)	338 (11%)	683 (11%)	0.51
Missing or unknown history of diabetes mellitus	14 (<1%)	23 (1%)	37 (1%)	
History of CHF	189 (6%)	228 (8%)	417 (7%)	0.12
Missing or unknown history of CHF	30 (1%)	37 (1%)	67 (1%)	

*Chi-square for proportions and t test for continuous variables

Less than 1% of the patients in each treatment arm had undergone PTCA in the past and approximately 1% in each arm had undergone CABG in the past.

Table 9. Physiological comparability of treatment groups

Characteristic	Outcome	rPA	SK	P-value*
Systolic BP (mm Hg)	n	2999	3000	0.08
	Mean ± SD	136 ± 23	135 ± 22	
Diastolic BP (mm Hg)	n	2991	2993	0.76
	Mean ± SD	81 ± 13	81 ± 13	
Heart rate	n	3000	3000	0.02
	Mean ± SD	77 ± 18	78 ± 18	
Killip class	I	2370 (80%)	2350 (80%)	0.79
	II	504 (17%)	530 (17%)	
	III	59 (2%)	53 (2%)	
	IV	19 (1%)	19 (1%)	

*Chi-square for proportions and t test for continuous variables

•Reviewer's comment: In general the patients appeared to be well balanced between the two arms with respect to baseline historical and physiological features. The vital sign distribution and history of hypertension were evenly divided between the two arms. The mean systolic BP of 135 -136 mm Hg in each arm of the trial was similar to the mean systolic BP of 130 mm Hg in patients enrolled in GUSTO-1. The prior MI history of 15% in the trial is similar to the 16% history noted in GUSTO -1 and the 20% incidence noted in the published meta-analysis by the Fibrinolytic Therapy Trialists' Collaborative Group. A history of diabetes mellitus was recorded in 10% of the patients analyzed in the meta-analysis and in 15% of the patients enrolled in GUSTO-1. The incidence of pre-existing CHF in the GUSTO-1 and the meta-analysis studies was not published. In general, the historical and physiological demographics of the

patients in this trial are consistent with other published reports ,except for the small number of noncaucasians enrolled.

4.2.3 Failure to Dose:

Table 10. Administration of trial medication

	rPA	SK	Total
Number randomized	3004	3006	6010
Treatment never started	38 (1.3%)	33 (1.1%)	71 (1.2%)
Treatment started but incomplete	61 (2%)	65 (2.2%)	126 (2.1%)
Treatment completed	2904 (97%)	2906 (97%)	5810 (97%)
Missing	1	2	3

71 patients did not receive trial medication. Of these 71 patients the most common reason for not receiving a trial medication was the discovery of an applicable exclusion criterion or misinformation regarding inclusion criteria (31 patients). Six of the 71 patients refused the trial medication. Other causes for failure to dose included: death (3 patients), technical reasons (eg., dropped kit) (8 patients), cardiac arrest or arrhythmia (12), "spontaneous lysis" (3 patients), stroke (1 patient), peripheral embolus (2 patients), and suspected aortic aneurysm (2 patients), TIA (2 patients) and nose bleed (1).

126 patients did not receive the complete dose of trial medication (rPA = 61 patients, SK = 65 patients). The reason for the incomplete dosing was not stated for 10 of the 126 patients. The most common causes for interruption of the dose include:

Table 11. Patients with Interrupted Doses

Reason	rPA	SK	Total
Hypotension	19 (33%)	13 (22%)	32 (28%)
Death	15 (26%)	11 (19%)	26 (22%)
Cardiac arrest	3 (5%)	7 (12%)	10 (9%)
Other*	21 (36%)	27 (47%)	48 (41%)
Total	58	58	116

*spontaneous lysis, consent withdrawn, peripheral emboli, technical problems, allergic symptoms, seizure

4.2.4 Concomitant Medication: Most patients (>90%, n = 6010) received both heparin and aspirin.

Table 12. Compliance with concomitant medications

	rPA	SK	Total
Initial aspirin use	2769 (92%)	2794 (93%)	5563 (93%)
No initial aspirin use	231 (8%)	206 (7%)	437 (7%)
Missing aspirin data	4	6	10
Initial heparin use	2954	2956	5910
No initial heparin use	9	12	21
Missing heparin data	2	3	5

The mean heparin dose in the first 24 hours was the same for both treatment arms, 27,000 (± 6,000) Units.

4.2.5 Confirmed Diagnoses: Most patients were definitively diagnosed as having an MI on the basis of EKG and CPK enzyme findings (5487, 91%). 224 patients were diagnosed as having a possible MI on the basis of CPK enzyme elevations above the normal range, but less than two times the normal limit.

Table 13. Patient myocardial infarction diagnoses

	rPA	SK	Total
Q wave MI	2260 (75%)	2297 (77%)	4557 (76%)
Non Q wave MI	475 (16%)	455 (15%)	930 (16%)
Possible MI	125 (4%)	99 (3%)	224 (4%)
Ischemic heart disease	98 (3%)	97 (3%)	195 (3%)
Chest pain, unknown	28 (1%)	36 (1%)	64 (1%)
Other	14 (1%)	16 (1%)	30 (1%)
Missing data	4	6	10
Total	3004	3006	6010

Most infarcts were assessed as inferior (3175 ,56%).

Table 14. Infarct site

Site	rPA	SK	Total
Anterior	1184 (41%)	1253 (44%)	2437 (43%)
Inferior	1624 (57%)	1551 (54%)	3175 (56%)
Undefined	31 (1%)	26 (1%)	57 (1%)
Anterior + Inferior	20 (1%)	20 (1%)	40 (1%)
Missing	1	1	2
Total	2860	2851	5711

•Reviewer's comment: Anterior ST segment elevation was noted in 43% (2601) of the patients while inferior ST segment elevation was noted in 54% (3265) of the patients. This compares to an incidence of 23% for anterior ST segment elevation and 28% inferior ST segment elevation in the patients in the meta-analysis published by the Fibrinolytic Therapy Trialists' Collaborative Group. This difference may be related to the varying EKG entrance criteria for the studies included in the meta-analysis. The ST segment elevation location of the patients enrolled in GUSTO-1 was not published. However, 39% of the GUSTO-1 patients had anterior infarctions, which is similar to the 43% incidence noted in this trial. Patients in the meta-analysis were not categorized by the location of their infarction.

5.0 Primary Endpoint Analysis:

The primary endpoint for the study was 35 day, all cause mortality.

5.1 Mortality Rate Analysis: The mortality rate at 35 days for all patients is shown below in Table 15.

Table 15. Mortality rate

	rPA	SK	Total
Alive	**2724 (91%)**	**2707 (90%)**	**5431 (90%)**
Dead	**270 (9.0%)** 95% CI:8.0, 10.0)	**285 (9.5%) *** 95%CI;8.5,10.6	**555 (9.23%)**
Missing data	10	14	24
Total Enrollment	3004	3006	6010

*p = 0.48, rPA vs. SK, Chi-square test

•Reviewer's comment: The 35 day mean mortality rate difference for rPA- SK is -0.51% and the one-sided 95% upper confidence limit for the difference is 0.77%. Since the lower boundary for the benefit of thrombolytics compared to placebo is 2.1% (from the meta-analysis), to retain 50% of the benefit of thrombolytics rPA must have a "harmful" effect on mortality of no greater than 1.05 percentage points. Since 0.77% is less than 1.05, rPA appears to have retained at least 50% of the benefit of thrombolytic therapy (compared to SK). In GUSTO -1 the 30 day mortality rate for SK + IV heparin was 7.4%. Of note, patients in GUSTO-1 had to be treated within 6 hours of onset of chest pain. As will be shown below, among those patients in INJECT treated within 6 hours of the onset of chest pain the SK 35 day mortality rate is 8.4% and the rPA mortality rate is 7.8%. In ISIS-3 (published in 1992,SK + aspirin + SC heparin, treatment within 24 hours of chest pain onset), the SK 35 day mortality rate was 10.5%. In the subgroup of patients in ISIS-3 receiving treatment with SK, aspirin and SC heparin within 6 hours of chest pain onset the mortality rate was 9.8%. These comparisons suggest that the observed SK mortality rate in INJECT (9.5% for patients treated within 12 hours of the onset of pain and 8.4% for patients treated within 6 hours of the onset of pain) may be slightly higher than what one might anticipate from this therapeutic regimen. However, it is within the range of mortality noted when SK is combined with SC heparin. Since recent recommendations include the use of either SC or IV heparin (or no heparin) with SK thrombolysis, the observed 9.5% SK mortality rate in INJECT seems tenable.[6]

The mortality rate across the countries is shown below, with the number of patients enrolled:

6. Gossage, JR. Acute myocardial infarction; reperfusion strategies. Chest 1994;106:1851-66.

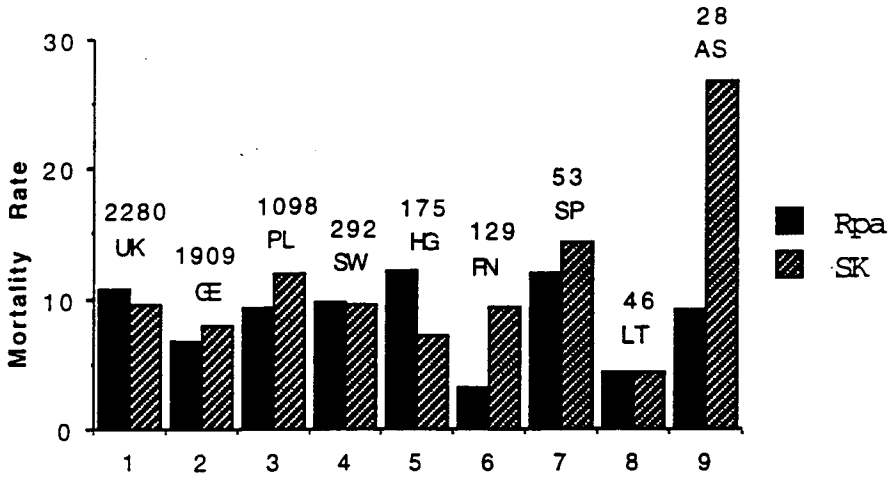


Figure 2. Mortality Rate by Country

Shown are the country (UK, Germany, Poland, Sweden, Hungary, Finland, Spain, Lithuania, Austria) and the total number of patients enrolled in each country.

•Reviewer's comment: There was no statistically significant difference in the mortality rates between the two arms of the clinical trial in any country. The wider mortality differences in countries enrolling less than 200 patients probably reflects chance variation due to the small number of patients. Of the 28 patients enrolled in AS, mortality data are missing for 2 patients. Of the remaining 26 patients, there were 4 deaths in the SK arm and 1 death in the rPA arm. Of the 175 patient enrolled in Hungary, mortality data are missing for 1 patient. Of the 174 remaining patients, there were 11 deaths in the rPA arm and 6 deaths in the SK arm.

5.1.1 Mortality Rate Sensitivity Analysis: As previously noted, there were 10 patients in the rPA arm with missing mortality data and 14 patients in the SK arm with missing mortality data. The following table (Table 16) examines the difference in rPA - SK mortality rates and the upper 95% confidence limit when it is assumed that there were additional deaths in the rPA arm.

Table 16. Sensitivity Analysis

Number of deaths in rPA arm	n	Mortality rate in rPA arm (%)	Difference in mortality rates (rPA - SK, %)	95% Upper confidence limit (%)
270	2994	9.02	-0.51	0.72
271	2995	9.05	-0.48	0.75
272	2996	9.08	-0.45	0.78
273	2997	9.11	-0.42	0.81
274	2998	9.14	-0.39	0.85
275	2999	9.17	-0.36	0.88
276	3000	9.20	-0.33	0.91
277	3001	9.23	-0.30	0.94
278	3002	9.26	-0.27	0.97
279	3003	9.29	-0.24	1.00
280	3004	9.32	-0.21	1.03

If it is assumed that the 14 patients with missing data in the SK arm are alive at 35 days and there were 280 deaths in the rPA arm, the difference in mortality rates (rPA - SK) would be -0.17% with the 95% upper confidence limit of 1.07%.

•Reviewer's comment: The sensitivity analyses support the initial primary efficacy endpoint findings. The "retention of 50% of the mortality benefit" concept is illustrated in Figure 3.

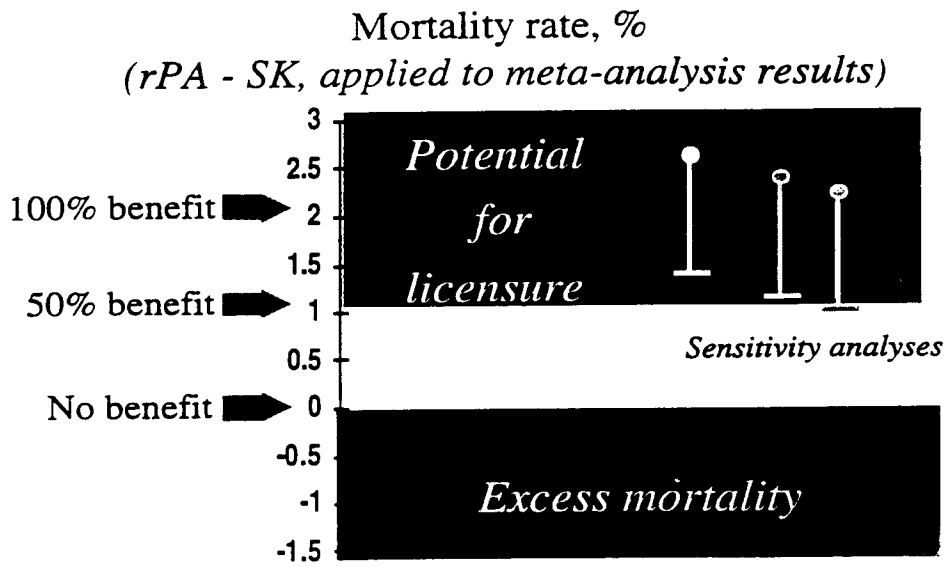
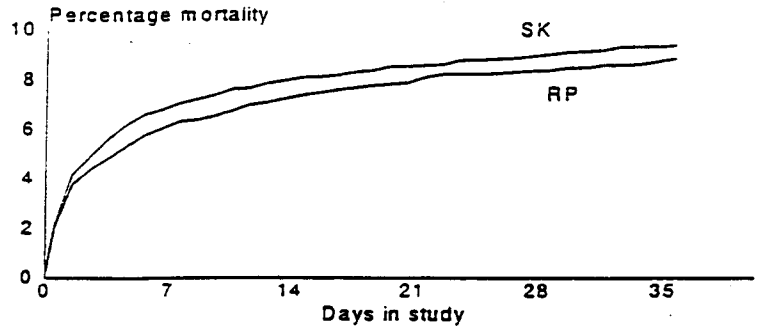


Figure 3. Mortality Rate Results with Sensitivity Analyses
The mortality point estimate and 95% CI result from INJECT is shown on the left and the two bars on the right indicate the hypothetical results from the sensitivity analyses assumptions.

5.1.2 Kaplan-Meier mortality curves: Using Kaplan-Meier mortality curve estimates, the 35 and 6 month mortality estimate rates and curves are shown below:



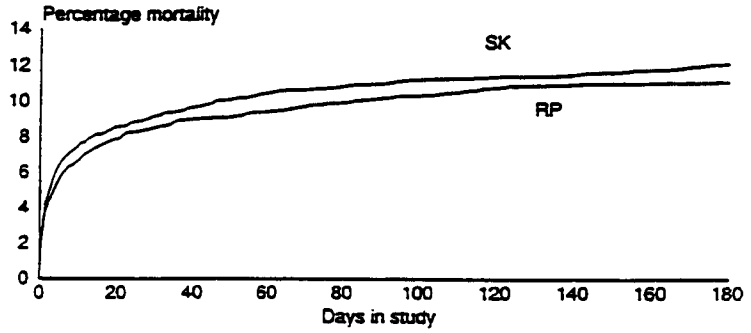


Figure 4. Mortality curves

148 (2.5%) of enrolled patients did not have 6 month mortality data.

The Kaplan-Meier curves show that the mortality rates begin to plateau at approximately 14 days following thrombolysis. The mortality rates within the first 24 hours of receiving medication were 3.1% for patients receiving rPA, compared to 3.8% for patients receiving SK (excluding the 71 patients who received neither agent).

5.2 Secondary Endpoint Analyses:

5.2.1 **The In-hospital Mortality Rates** for patients receiving some trial medication are shown below:

Table 17. Death in hospital, patients receiving some trial medication

	rPA, n = 2964	SK , n = 2971
Deaths in hospital	237 (7.9%)	256 (8.5%)*
Missing data	2	1

P = 0.38, Chi-square test

•Reviewer's comment: The duration of hospitalization varied considerably from center to center and from country to country. Among all enrolled patients, the mean and SD of hospitalization was: rPA13.71 (±9.09) days

SK 13.81 (±9.21) days
p = 0.48

Centers were significantly different with respect to duration of hospitalization, but there was no interaction between center and treatment groups. That is, within each center, the number of days "in hospital" was not different for the two treatment arms. UK had the smallest number of days (rPA/SK: 7.2/7.5 days) while Germany had the longest (rPA/SK: 20.8/20.7 days).

5.2.1.1 Cause of Death: The site investigator reported the cause of death for all patients who died in the hospital. There was no centralized assessment of death and the criteria for classification of the cause of death were not stated in the clinical protocol.

Table 18. Cause of death at 7 days following thrombolysis

	Number of deaths at 7 days following thrombolysis	Due to shock or electro-mechanical dissociation	Due to cardiac rupture	Due to asystole	Other*	Missing data
rPA	195	107 (55%)	28 (14%)	17 (9%)	42 (22%)	1
SK	214	113 (53%)	33 (15%)	28 (13%)	40 (19%)	1

*found dead, stroke, noncardiac

•Reviewer's comment: The assignment of the cause of death is not likely to be reliable across the investigational sites since there were no consistent criteria for determination of the cause of death.

5.2.2 Six Month Mortality: The Kaplan-Meier estimates of six month mortality for all patients are shown in Table 19.

Table 19. Kaplan-Meier estimates of six month mortality

	estimate (%)	95% CI	number of deaths at 6 months (698 total)
rPA	11.14	10.01, 12.27	332
SK	12.15	10.98, 13.32	366

5.2.2.1 Variation in Mortality Rates during the Course of Treatment: During the 14 month course of the trial the 35 day mortality rates varied from quartile to quartile (Table 20).

Table 20. Mortality by enrollment quartile

Recruitment quartile	rPA		SK		Total	P*
	enrolled, n	mortality, %	enrolled, n	mortality, %	n	
1	748	9.9%	760	7.5%	1508	0.10
2	764	9.3%	728	10.3%	1492	0.51
3	740	7.7%	760	9.0%	1500	0.39
4	742	9.2%	744	11.4%	1486	0.15
number of patients missing data	10	-	14	-	24	-
Total	3004	9.0%	3006	9.5%	6010	0.48

*Chi-square test, rPA vs SK mortality

•Reviewer's comment: Although not statistically significant, the first quartile mortality rates for rPA exceeded those for SK. The sponsor attributes this to the exceptionally low mortality rate (chance variation) for SK during this quarter. Using statistical modeling the sponsor shows that this variation is related to the SK mortality rate variation and not to the rPA mortality rate variation. This is of note, since most patients in the first quarter received rPA manufactured by the ——— (61%). rPA manufactured using the ——— was used most commonly in the subsequent quarters. Of some interest is that earliest enrollment, by countries, was greatest for the UK and Germany. 26% of all patients enrolled by either Germany or the UK were enrolled in the first 5 months of the trial, while 15% of patients enrolled by other countries were enrolled in the first 5 months of the trial. To examine this further the mortality rates for the UK and Germany were examined by quartile (Table 21). If the SK mortality rates remained consistently lower than the rPA mortality rates in these countries (an opposite finding from the overall results) questions regarding other covariables (such as medical practice patterns) could be raised.

Table 21. UK and Germany enrollment and promoter use by enrollment quartiles

Recruitment quartile	Germany enrollment	Germany mortality rate %		UK enrollment	UK mortality rate %		——— : ———
	n, % of quartile	rPA	SK	n, % of quartile	rPA	SK	%
1	631 (42%)	5.5%	6.23%	561 (37%)	13.2%	8.3%	61%
2	437 (29%)	5.5%	6.2%	629 (42%)	11.0%	9.6%	16%
3	400 (27%)	7.9%	6.1%	593 (40%)	7.0%	10.4%	8%
4	439 (30%)	5.5%	10.9%*	485 (33%)	12.1%	10.1%	3%

* P = 0.04, Chi-square test (all other mortality rate comparisons are P > 0.05)

•Reviewer's comment: Of some concern was the possibility that the variation in SK mortality rate across the quartiles (and especially in the fourth quartile) may have been related to enrollment of patients in countries other than the UK or Germany and not experienced in the use of SK thrombolysis (making an analogy to the USA inappropriate). However, the above table demonstrates that the higher SK mortality rate in the fourth quartile was also noted in Germany. It seems likely that the variation in SK mortality rate is related to chance alone.

Table 22. Promoter use and mortality rates at 35 days

Promoter	rPA		
	number of patients treated	deaths	mortality rate*
———	661	66	10.0%
———	2333	204	8.7%

*P = 0.67, Chi-square test

•Reviewer's comment: Table 22 demonstrates no statistically significant difference in the rPA mortality rate based on the promoter used in manufacturing. Together, these data support the contention that the variation in mortality rates across the quartiles during the clinical trial was insignificant.

5.2.3 In-hospital Incidence of Stroke: The incidence of stroke (defined as a neurological event resulting in death or disability in the study report, but not defined in the clinical protocol) at various time points is shown in Table 23.

Table 23. Stroke incidence

Event	rPA n = 3004‡		SK n = 3006‡		P*
	number of patients with strokes	%	number of patients with strokes	%	
Strokes, in-hospital	**37**	**1.23**	**30**	**1.01**	**0.44**
--hemorrhagic	23	0.78	11	0.37	0.04
--embolic	10	0.30	9	0.30	0.82
--uncertain	4	0.13	10	0.34	0.18
Strokes, discharge-35 days	**5**	**0.17**	**3**	**0.10**	**0.72**
--hemorrhagic	0	0	1	0.10	0.32
--embolic	5	0.17	1	0.03	0.22
--uncertain	0	0	1	0.03	-
--death by 35 days	1	0.03	0	0	-
Total stroke to day 35	**42**	**1.4**	**33**	**1.1**	**0.42**
Stokes, day 35-180	0	0	2	0.1	-
Total stroke to day 180	**42**	**1.4**	**35**	**1.16**	**0.42**

*Chi-square test

‡5 patients from rPA group and 4 patients from SK group with missing data

•Reviewer's comment: In two rPA cases, the diagnosis of hemorrhagic stroke was made on the basis of clinical criteria alone, without CT or MRI scanning. All other diagnostic causes for stroke were confirmed by CT or MRI. The statistically significant difference in the in-hospital hemorrhagic stroke rate may be related to the large number of "uncertain" types of strokes in the SK group. Of the 8 strokes that occurred in patients following discharge (but prior to the 35 day follow up point) the number that resulted in disability was not stated. The protocol stated that the secondary endpoint analysis would be related to the "in-hospital" incidence of stroke. Of note, the SAS data sets reported a total of 35 strokes among the SK patient population by day 35. The sponsor states that two of these strokes were incorrectly categorized in the SAS data sets. The above table is correct.

With 3000 patients per arm of the trial and alpha = 0.05 and power = 0.80, the trial could detect a doubling of the stroke rate from 1% to 2%. (Specifically to detect a difference of incidence of 1% vs 2% between two arms of the trial, each arm would need 2515 patients). Overall, the trial was not powered adequately to detect a 50% increase in the stroke rate (assuming the baseline incidence is 1%). The trial was powered adequately to reasonably exclude a 100% increase in the stroke rate (assuming the baseline incidence is 1%).

Disability was determined only for in-hospital strokes. The outcome of patients suffering in-hospital strokes is shown in Table 24.

Table 24. Stroke outcome

Event	rPA n = 3004‡		SK n = 3006‡		P*
	number of patients with event	%	number of patients with event	%	
Strokes, in hospital	37	1.23	30	1.01	0.44
-death by 180 days	22	0.73	13	0.43	0.18
-disabled at 180 days	5	0.17	8	0.27	0.58
-recovered at 180 days	9	0.3	9	0.3	1.00

*Chi-square test
‡adjusted for 5 patients from rPA group and 4 patients from SK group with missing data

•Reviewer's comment: Of note is that the determination of disability was based on the functional assessment performed 6 months following thrombolysis. In GUSTO-1, the assessment of disability was determined at hospital discharge. It would be expected that the incidence of disabling stroke in INJECT might be lower than that in GUSTO -1 because of the longer period of recovery permitted in the INJECT trial. (In GUSTO-1 the SK total stroke rate was 1.4% and the nonfatal, but disabling stroke rate was 0.5%). Hence, it is also important to examine the combined endpoint of day 35 death or nonlethal stroke, in addition to the analysis of death or disabling stroke, since 6 months of functional impairment (followed by recovery) may be interpreted as a degree of negative clinical benefit.

5.2.3.1 Combined Endpoint of Death or Stroke by 35 Days: The following table illustrates the combined endpoint of stroke + death or disabling stroke + death.

Table 25. Death or stroke by 35 days

Event	rPA n = 3004‡		SK n = 3006‡		P*
	n	%	n	%	
Mortality or disabling stroke	275	9.2	293	9.8	0.64
Mortality or stroke	292	9.7	309	10.3	0.47

*Chi-square test
‡adjusted for 24 patients missing 35 day mortality status; 9 patients missing stroke data

•Reviewer's comment: These data illustrate that the primary endpoint is consistent with the results of a "net clinical benefit" analyses. It is impossible to define "net clinical benefit" as death or "disabling" stroke at 35 days since the determination of disability was made at six months. The Table 25 should be interpreted cautiously since mortality refers to 35 day outcome but disabling stroke refers to a six month outcome. However the "mortality or stroke" does refer to a 35 day outcome.

5.2.4 35 Day Outcome by Prospectively Stated Subgroups: Of the multiple factors analyzed, the incidence of elevated systolic blood pressure and history of prior MI were statistically significantly different.

Table 26. Mortality by prospectively stated subgroups

Characteristic	Category n	rPA		SK		P*
		number of deaths	%	number of deaths	%	
Sex	male (4328)	150	7.0	159	7.31	0.69
	female (1655)	120	14.2	125	15.4	0.49
Age	≤ 50 yrs (943)	9	1.9	13	2.8	0.40
	51 - 65 yrs (2418)	60	4.8	72	6.1	0.17
	> 65 yrs (2617)	201	15.7	198	14.8	0.51
Time of symptom onset to start of thrombolysis	≤ 3 hrs (2505)	83	6.7	94	7.5	0.42
	3 - 6 hrs (2243)	100	9.1	107	9.4	0.79
	> 6 hrs (1141)	78	13.2	75	13.6	0.83
Systolic BP	≤ 160 mm Hg (5364)	229	8.6	264	9.7	0.11
	> 160 mm Hg (614)	40	12.0	19	6.8	< 0.01
EKG diagnosis	Anterior ST elevation (2593)	150	11.9	165	12.4	0.42
	Inferior ST elevation (3252)	107	6.5	104	6.5	0.89
	Bundle branch block (108)	13	21.3	11	23.4	0.84
Prior MI	Yes (872)	49	11.3	76	17.3	0.01
	No (5016)	212	8.5	201	8.0	0.56
	Unknown (94)	9	16.4	6	15.4	0.90

*Chi-square test

•Reviewer's comment: Subgroup analyses of the primary endpoint were not listed as secondary endpoints in the original clinical protocol but certain subgroup analyses were planned in the original protocol. These prospectively stated subgroup analyses included sex, age, time since onset of MI, prior MI, location of infarction and systolic blood pressure. Other subgroup analyses were not prospectively stated. At baseline, the SK and rPA arms were balanced with respect to history of prior MI (14-15%). This incidence is similar to the incidence noted in the GUSTO -1 treatment arms (16-17%). In INJECT, for the patients with a history of a prior MI, the SK mortality rate (17.3%) was higher than that for rPA (11.3%). The history of prior

MI was not a prespecified subgroup for analysis in GUSTO-1 . In the meta-analysis performed by the Fibrinolytic therapy trialists' collaborative group, the 35 day mortality for placebo- arm patients with a history of prior MI was 14.1%, while the thrombolysis-arm patients with a history of prior MI had a mortality rate of 12.5%. The 21-day mortality rate for patients with prior MI was 17% for both SK and placebo in GISSI (two arm study of SK vs placebo in 11,800 patients). [7] *The five week mortality rate for SK and placebo were 13% and 17%, respectively in ISIS-2 (4 arm study of SK, SK + aspirin, aspirin alone, placebo in 17,200 patients).*[8] *No reason, other than chance seems responsible for the high SK mortality rate (similar to GISSI rate).*

The mortality rate for patients treated with rPA within 6 hours of the onset of symptoms was 7.8% and was not significantly different from the 8.4% mortality rate for SK patients. In GUSTO (thrombolysis was to be administered within 6 hours of symptom onset), the SK mortality rate (with IV heparin) was 7.4%. As previously noted, prior clinical trials have shown a slightly higher mortality rate for SK patients treated within 6 hours of symptom onset, depending somewhat on the adjunctive therapies. The observed mortality rate for SK patients treated within 6 hours of symptom onset is not alarmingly inconsistent with prior clinical trial experience.

In the previously referenced meta-analysis, the placebo-control mortality rate for patients with a SBP 150-174 was 8.7% and for patients with a SBP >174 the placebo mortality rate was 8.2%. The corresponding mortality rates for thrombolytic-treated patients were approximately 1% (absolute % points) less. Why the mortality rate for patients with a SBP > 160 treated with rPA (12%) in INJECT is twice that of SK-treated patients, and also higher than that noted in the meta-analysis is not clear. The meta-analysis did show that the mortality benefit for thrombolysis decreased for patients with systolic hypertension.

In INJECT, the in-hospital stroke rate was approximately twice as high for patients with SBP > 160 who received rPA (2.4%) as that for patients with SBP > 160 who received SK (1.1%). However, the number of strokes in these analyses are small (8 for rPA, 3 for SK). The 59 deaths in the subset of patients with a SBP >160 had complete case report forms submitted and reviewed. All 59 patients were caucasian or asian. 43% of the patients in each (rPA and SK) arm were male. No patient had a diastolic BP > 100 mm Hg. 58% of the 40 rPA -treated patients had anterior MI, while 68% of the SK -treated patients had anterior MI. 50% (20/40) of the rPA-treated patients died within 48 hours of thrombolysis, compared to 32% (6/19) of the SK-treated patients. There were four patients who died of intracerebral hemorrhage in the rPA arm and no patients with intracerebral hemorrhage in the SK arm. No other findings appeared remarkable from a review of the CRF.

The median systolic blood pressure among all enrolled patients was 135 mm Hg. The following table examines other blood pressure dichotomies.

Table 27. Incidence of stroke and death among patient subsets by blood pressure categories

Blood pressure subgroup	n	Number of patients with a stroke; n (%)		P*	Number of patient deaths:n (%)		P*
		rPA	SK		rPA	SK	
SBP ≤ 135 mm Hg	3036 for stroke 3023 for death	20 (1.3%)	14 (0.92%)	0.29	139 (9.2%)	176 (11.6%)	0.03
SBP > 135 mm Hg	2960 for stroke 2953 for death	22 (1.5%)	21 (1.4%)	0.89	129 (8.7%)	106 (7.2%)	0.13
DBP > 80 mm Hg	2583 for stroke 2576 for death	16 (1.3%)	20 (1.5%)	0.56	110 (8.7%)	108 (8.3%)	0.73

*Chi-square test

7. GISSI Study Group. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;397-401.

8. ISIS Study Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction:ISIS-2. Lancet 1988;349-360.

There was one death among the 32 patients who had a diastolic blood pressure recorded as > 100 mm Hg.

5.2.4.1 35 Day Mortality Exploratory Analysis of Additional Subgroups: The following analyses (Table 28) were not prospectively stated in the clinical protocol.

Table 28. Exploratory Analyses of mortality rates

Characteristic	Category n	rPA		SK		P*
		number of deaths	%	number of deaths	%	
Weight	≤ 65 kg (1058)	64	11.7	68	13.3	0.42
	> 65 kg (4248)	141	6.7	154	7.2	0.47
Smoking history	Yes (2685)	71	5.3	76	5.6	0.73
	No (1979)	131	13.4	134	13.4	0.97
	Ex (1297)	64	9.5	66	10.6	0.52
Diabetes	Yes (682)	49	14.2	51	15.1	0.76
	No (5207)	219	8.3	231	8.8	0.54
	Unknown (28)	2	18.2	1	5.9	0.30
Heart failure history	Yes (417)	41	21.7	55	24.1	0.56
	No (5506)	223	8.0	220	8.1	0.97
	Unknown (57)	6	22.2	8	26.7	0.70
Hypertension history	Yes (1988)	118	11.6	108	11.1	0.78
	No (3890)	148	7.7	168	8.6	0.33
	Unknown (103)	4	8.3	7	12.7	0.47
Angina history	Yes (1865)	122	12.5	125	14.1	0.32
	No (4029)	143	7.3	150	7.3	0.99
	Unknown (87)	5	10.2	8	21.1	0.16
PTCA history	Yes (48)	4	19.1	1	3.7	0.08
	No (5931)	266	9.0	282	9.5	0.45

CABG history	Yes (74)	4	9.3	5	16.1	0.38
	No (5897)	265	9.0	277	9.4	0.62
	Unknown (10)	1	16.7	1	25.0	0.75
Prior β blocker use	Yes (855)	43	9.6	60	14.8	0.02
	No (5125)	227	8.9	222	8.6	0.67
	Unknown (27)	0	0	3	20.0	-
Confirmed MI location by EKG	Anterior (2434)	145	12.3	162	12.9	0.63
	Inferior (3163)	106	6.5	100	6.5	0.94
	Undefined (58)	7	21.9	9	34.6	0.28
	Anterior + Inferior (40)	6	30.0	4	20.0	0.47

*Chi-square test

Since rPA is proposed for use as a fixed dose (not weight adjusted), Table 28 examines the mortality for patients in various weight categories.

Table 29. 35 day mortality rates by weight

Weight (n)	rPA		SK		P*
	n	%	n	%	
< 60 kg (566)	48	16.3	53	19.5	0.31
> 60 kg (4740)	242	10.2	272	11.5	0.16
not recorded (689)	65	19.5	63	17.7	0.93

*Chi-square test

•Reviewer's comment: As has been shown in other trials of thrombolytics, mortality rates for patients with low weights are higher than for patients with higher weight. There was no statistically significant difference in the mortality rates for low weight patients in INJECT, when rPA was compared to SK.

5.2.4.2 Multivariate Analysis of 35 Day Mortality: The subset analyses of the mortality rates showed that 35 day mortality rates were different between males and females, between young and old, between low weight and higher weight patients. The mortality rates were also dependent upon the time from symptom onset to treatment. A logistic model was formed entering age, weight and time to treatment as continuous variable and sex as a dichotomous variable along with the treatment effect. None of the interaction effects were significant. Patient weight was not found to be a significant factor. Reciprocal, log and square of weight were also applied in the model. None of these were found to be significant for predicting 35 day mortality. The final logistic model contained these variables along with the treatment. The results of the model are shown in Table 30.

Table 30. Results of logistic regression analysis

Variable	Parameter estimate	Standard error	Odds ratio	P value
Intercept	7.74	0.3671	-	0.0001
Treatment	-0.0660	0.0937	0.936	0.48
Sex	-0.3675	0.0978	0.692	0.0002
Age	-0.0684	0.0048	0.934	0.0001
Time to treatment	-0.0728	0.0165	0.930	0.0001

The odds ratio provides an estimated risk of death as 6.8% less with rPA therapy than with SK therapy. The risk of death for female patients is 44.5% more than for male patients. Using age and time to treatment as continuous variables, an unit increase in age (year) increases the risk of death by 7.1%. Each increase in time to treatment by one hour increases the risk of death by 7.5%.

•Reviewer's comments: The estimates from this modeling result are consistent with findings from other clinical trials of thrombolytics.

5.2.5.1 In-hospital Incidence of Intervention Therapy: The incidence of the use of coronary artery bypass grafting (CABG) and/or angioplasty (PTCA) and/or additional thrombolysis is shown in Tables 30 and 31.

Table 31. In-hospital interventions

Intervention	rPA		SK		P*
	n	%	n	%	
CABG	15	0.5	25	0.8	0.15
PTCA	133	4.4	142	4.7	0.62

*Chi-square

Table 32. Interventions within 180 days of thrombolysis

Intervention	rPA		SK		P*
	n	%	n	%	
CABG	62	2.1	68	2.3	0.60
PTCA	223	7.4	227	7.6	0.80

*Chi-square

Table 33. Additional thrombolysis, in-hospital

Additional thrombolysis	rPA		SK		P*
	n	%	n	%	
Yes	111	3.7	116	3.9	0.79
No	2888	96.3	2885	96.1	N/A

*Chi-square

In half the cases the additional agent was tPA, with the remainder receiving either SK or urokinase.

•Reviewer's comment: In GUSTO-1, there was a 15% 30 day incidence of PTCA and a 9% 30 day incidence of CABG. The comparable rates were less than half these in INJECT. This difference probably reflects practice patterns, but conceivably could also influence mortality rates.

5.2.5.2 In-hospital Use of Additional Medication: The use of medications during the initial hospitalization is shown in Table 34.

Table 34. In-hospital medications

Medication	rPA		SK		P*
	n	%	n	%	
diuretics, CHF	920	31	1013	34	0.01
Ace inhibitors, CHF	664	22	667	22	0.92
Cardiac glycoside	257	8.6	321	11	0.01
anti-arrhythmics	486	16	516	17	0.30
oral beta blockers	1648	55	1585	53	0.10
IV beta blockers	227	7.6	252	8.4	0.23
Ca channel blockers	501	17	452	15	0.09
Subsequent aspirin	2785	93	2767	92	0.35
oral anticoagulants	298	10	300	10	0.94
oral nitrates	1835	61	1819	61	0.67
IV nitrates	1703	57	1742	58	0.31

*Chi-square test

•Reviewer's comment: Notable among these findings is the use of diuretics and beta blockers. Approximately 1/3 of all the patients were treated with diuretics for suspected CHF during their hospitalization. At study entry, approximately 5% (294) of all the patients were receiving diuretics for CHF and approximately 7% (417) of all the patients had a history of CHF. The high use of diuretics somewhat correlates with the approximately 25% incidence of CHF diagnosed during the hospitalization. The incidence of CHF was balanced between the two treatment groups. The 25% incidence of CHF in INJECT compares to the 17% incidence detected in GUSTO.

14% of the patients were taking beta blockers orally prior to their admission to the hospital. 50% of the patients were prescribed beta blockers during their hospitalization. This compares to the use of oral beta blockers in 71% of the patients enrolled in GUSTO. The 8% use of IV beta blockers in INJECT is notably lower than the 46% use among patients enrolled in GUSTO.

5.2.6 In-hospital Incidence of Reinfarction: The incidence of reinfarction, at various time points, among all patients is shown below:

Table 35. Reinfarction

Reinfarction	rPA		SK		P*
	n	%	n	%	
In-hospital	151	5.0	163	5.3	0.45
Discharge-35 days	45	1.5	34	1.1	0.21
35-180 days	6	0.2	2	0.1	0.16
Total	202	6.7	199	6.6	0.87

*Chi-square test

5.2.7 In-hospital Incidence of Congestive Heart Failure:

Table 36. Congestive heart failure

Congestive heart failure	rPA		SK		P*
	n	%	n	%	
In-hospital	708	24	791	26	0.01
Discharge-35 days	46	1.5	69	2.3	
Total to day 35	754	25.1	860	28.6	0.01

*Chi-square test

•Reviewer's comment: The definition of congestive heart failure was not stated in the protocol. The CRF s required the investigator to check "CHF/pulmonary edema" yes or no for both the in-hospital course and for the 35 day follow up period. These findings are consistent with the use of medications used to treat heart failure and support the contention that the incidence of heart failure in patients treated with rPA was not greater than that in patients treated with SK.

5.2.8 In-hospital Incidence of Non-cerebral Bleeding Events:

Table 37. Patients receiving study medication (n = 5936) and experiencing bleeding events

Bleed type	rPA		SK		P*	Total, n (%)
	n	%	n	%		
All events	451	15.2	460	15.5	0.77	911 (15.3%)
Required transfusion	26	0.9	35	1.2	0.25	61 (1.0%)
Classified as fatal	1	0.03	2	0.07	0.56	3 (0.05%)
"serious" (fatal/transfusion/prolonged hospitalization)	37	1.25	44	1.5	0.44	81 (1.4%)

•Reviewer's comments: Noncerebral bleeds were classified on the CRF according to the location, and then subclassified as :
-either "fatal/required transfusion" or "life-threatening/prolonged hospitalization"
or
-other.
In the analysis of bleeding events the sponsor considers the "fatal/required transfusion " and the "life-threatening/prolonged hospitalization" categories as "serious" bleeds. All other bleeds are considered "nonserious."

The approximately 1% incidence of serious bleeding detected in INJECT compares to the (approximately) 6% incidence of serious bleeding (ie., bleeding requiring transfusion) detected among patients in the various arms of the GUSTO trial.

There were a total of 1088 bleeding events reported in a total of 911 patients. The site of these bleeds is shown below:

Table 38. Bleeding Sites (n = bleeding events)

Site	rPA, n (%)	SK, n (%)	Total, n (%)
Puncture site	135 (4.6%)	151 (5.1%)	286 (4.8%)
Hemoglobin drop	75 (2.5%)	96 (3.2%)	171 (2.9%)
Gastro-intestinal	77 (2.6%)	83 (2.8%)	160 (2.7%)
Subcutaneous	67 (2.3%)	63 (2.1%)	130 (2.2%)
Genito-urinary	48 (1.6%)	56 (1.9%)	104 (1.7%)
Oral	54 (1.8%)	26 (0.9%)	80 (1.3%)
Epistaxis	27 (0.9%)	14 (0.5%)	41 (0.7%)
Hemoptysis	14 (0.5%)	16 (0.5%)	30 (0.5%)
Other (eye, muscle, retroperitoneal, pericardium)	46 (1.6%)	40 (1.3%)	86 (1.4%)
Total	543	545	1088

•Reviewer's comment: There were a total of 61 patients receiving transfusions in INJECT. This 1% incidence of transfusion is remarkably lower than the 10% incidence of transfusion noted in GUSTO and may be related to multiple factors (such as medical practice patterns).

5.2.9 Formation of antibodies against rPA: Baseline and follow-up blood tests (> 10 days post thrombolysis) were available for 1928 patients (65% of those receiving rPA) treated with rPA. No samples were positive for antibodies.

5.3 Additional Safety Findings:

The weight-related incidence of stroke and bleeding is shown below.

Table 39. Patients with strokes stratified by weight

Weight (n)	Stroke				P*
	rPA		SK		
	n	%	n	%	
≤65 kg (1061)	8	1.5	6	1.2	0.79
65 - 90 kg (3593)	23	1.3	20	1.1	0.11
> 90 kg (667)	3	0.9	1	0.3	0.37
Missing weight (689)	8	2.4	8	2.3	1.00

*Chi-square test

Table 40. Patients with bleeds stratified by weight

Weight (n)	Bleed				P*
	rPA		SK		
	n	%	n	%	
≤ 65 kg (1061)	112	20.6	109	21.4	0.72
65 - 80 kg (2449)	192	15.8	187	15.5	0.83
> 80 kg (1811)	110	12.4	120	13.2	0.63
Missing weight (689)	37	11.1	44	12.3	0.50

*Chi-square test

The number of patients experiencing AE and the type of AE are described below. Listed are all AE with an incidence ≥ 0.5 %.

Table 41. Patients experiencing additional AE
(exclusive of heart failure, bleeds, strokes, recurrent MI, deaths)

AE	rPA		SK		P*
	n	%	n	%	
Angina/myocardial ischemia	751	25.3	748	25.2	-
Hypotension	456	15.4	524	17.6	0.02
Ventricular tachycardia	230	7.8	239	8.0	-
Atrial fibrillation/flutter	213	7.2	258	8.7	0.03
Cardiac arrest (asystole, EMD)	179	6.0	211	7.1	0.11
Cardiogenic shock	136	4.6	173	5.8	0.04
Ventricular fibrillation	132	4.5	158	5.3	-
Third degree AV block	111	3.7	120	4.0	-
Supraventricular tachycardia	102	3.4	107	3.6	-
Bradycardia	73	2.5	59	2.0	0.25
Second degree AV block	58	2.0	51	1.7	-
Other arrhythmia	48	1.6	50	1.7	-
Allergic reaction	34	1.1	49	1.6	0.12
Hemopericardium	33	1.1	42	1.4	-
TIA or PRIND (cerebral ischemia)	21	0.7	19	0.6	-
Pulmonary embolus	14	0.5	4	0.1	< 0.01
Kidney failure	10	0.3	6	0.2	0.45
Pneumonia	9	0.3	17	0.6	-
Nausea	10	0.3	5	0.2	0.30
Upper respiratory infection	5	0.2	6	0.2	-
Hyperglycemia	5	0.2	1	0	-
Dizziness	3	0.1	0	0	-
Diarrhea	2	0.1	2	0.1	-
Confusion	2	0.1.	0	0	-
Dyspnea	1	0	3	0.1	-
Anaphylaxis	0	0	3	0.1	-

*Reviewer's comment: The case report forms were designed to track certain specific AE (stroke, other

cerebrovascular events, hemorrhages, heart failure and other cardiovascular events, deaths and allergic reactions. Other AE were reported at the discretion of the investigator in an "other" category. Hence, the safety review is probably most reliable for those specific events tracked on the case report forms. In general, the most crucial AE were those specifically tracked by the sponsor and the CRF were well designed to capture these events. Of note, during the conduct of the trial at least one allergic reaction to rPA was initially felt to be an anaphylactic reaction and resulted in a letter to the investigators (from the sponsor). This anaphylactic reaction was later reclassified (during the review of all AE by the sponsor) as an allergic reaction. Hence, the distinction of "allergic reaction" from anaphylaxis is somewhat arbitrary. In general, no novel safety concerns are posited by these data.

5.4 INJECT summary and reviewer's comment: *INJECT compared the safety and efficacy of rPA to SK in patients with AMI. There was a total of 6,010 patients enrolled, 3004 randomized to rPA and 3006 randomized to SK. Outcome data are missing for 10 rPA patients and 14 SK patients. By 35 days following thrombolysis there were 555 deaths (rPA 270 and SK 285). All cause mortality for patients at 35 days was 9% (95% CI 8.0,10.0) and 9.5% (95% CI 8.5, 10.6) for rPA and SK, respectively. The one-sided confidence limit around the mortality differences satisfied the FDA's contention that a new thrombolytic should retain at least 50% of the benefit effect of the comparator (using data from a meta-analysis of placebo-controlled studies). In INJECT the SK mortality data are in line with prior clinical trial experience. GUSTO-1 suggested that an accelerated tPA arm might be a better comparator. However, the results of GUSTO-1 were not known at the time INJECT was designed.*

By 35 days following thrombolysis there were 75 recorded strokes (rPA 42 and SK 33). The stroke rate by day 35 was 1.4% for rPA and 1.1% for SK. The difference in the stroke rate (rPA - SK) is 0.3 with a 95% CI of -0.26 and 0.86. INJECT was powered adequately to detect a doubling of the stroke rate for rPA compared to SK (assuming a baseline rate of 1%).

INJECT was a study conducted entirely in Europe and certain findings may be related to practice patterns or the patient population. For example, very few interventions were performed. Only 2% of the patients had CABG and only 8% had PTCA. There was also a strikingly low transfusion rate (less than 1%), even though the incidence of "serious" bleeding (1.5%) was actually higher than noted in GUSTO-1. Additionally, the safety and efficacy of rPA in noncaucasians cannot be stated from INJECT. However, the available published literature describing ethnic or racial differences in thrombolytic safety or efficacy is very small. The number of noncaucasians included in thrombolytic clinical trials has been relatively small (approximately 9% in GUSTO-1). One study has suggested that African-origin patients may have an enhanced fibrinogenolytic response to tPA which may correlate with a greater risk.[9] However, this study examined only 24 African-origin patients. Another published report (involving 174 Hispanics patients and 174 patients of African-origin) suggested that the greater fibrinogenolysis detected in the minority patient populations was clinically insignificant and suggested that thrombolytic safety and efficacy did not differ based on ethnicity or race.[10]

Overall, INJECT supports the contention that rPA is not worse than the Streptase™ brand of SK with respect to safety or efficacy.

6.0 Detailed Review of RAPID I (MF 4255)

6.1 Overview of RAPID 1:

" A randomized, open label, dose-response study to evaluate the effects of Reteplase at doses of 15 MU, 10 + 5 MU and 10 + 10 MU, relative to 100 mg tPA (Alteplase) on coronary artery patency and safety in patients with acute myocardial infarction." This is the primary dose ranging study and was conducted between August, 1991 and July, 1993 (last 1 month follow up of last patient). A total of 606 patients were randomized to one of four arms--three doses of rPA vs. one dose of tPA (Alteplase, standard administration over 3 hours). The primary endpoint was infarct-related artery (IRA) patency (TIMI 2

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9. Sane, DC, Stump, DC, Topol, EJ, et al. Racial differences in responses to thrombolytic therapy with recombinant tissue-type plasminogen activator. Circulation 1991;83:170-75.

10. Taylor, HA, Chaitman, BR, Rogers, WJ., et al. Race and prognosis after myocardial infarction. Circulation 1993;88:1484-94.

or 3) at 90 minutes following the initiation of thrombolysis. All rPA used in this trial was produced using the TAC promoter.

6.2 Investigators/Sites/Monitoring:

606 patients were enrolled at a total of 38 sites. The monitoring of selected sites was performed by a contract research organization, C [illegible], as well as by Boehringer Mannheim clinical research associates.

Two core angiographic laboratories were used in the review of arteriograms: for the USA, C [illegible] 1 18 arteriograms were reviewed by both laboratories to assess the consistency of interpretation. The TIMI grade assessment of the IRA was the same for 17/18 arteriograms.

6.3 IRB/CF:

All studies were approved by the local IRB and/or ethics committees and all patients provided informed consent.

6.4 Design:

Open-label, randomized, multinational, multicenter, parallel group study comparing the safety and patency-effect of three rPA doses to that of a 3 hour infusion of tPA (Alteplase). The original clinical protocol was dated June 20, 1991. There were two amendments. The first, dated August 13, 1991 allowed for the inclusion of fertile women who were using contraceptives. The second, dated November 22, 1991 allowed for the weight adjusted dosing of rPA and tPA.

6.5 Inclusion criteria:

-ages 18 through 75 years
-ST segment elevation ≥ 0.1 mV in 2 of 3 inferior leads or ≥ 0.1 mV in leads I and aVL or ≥ 0.2 mV in 2 contiguous precordial leads
-30 minutes of chest pain
-less than 6 hrs since onset of chest pain

6.6 Exclusion criteria:

-left bundle branch block
-prior CABG
-prior transmural myocardial infarction in the same area at any time or prior transmural infarction in a different area within the past month
-PTCA within the past two weeks
-prior CVA or TIA
-unexplained head pain or visual disturbance that may indicate intracranial bleeding
-active internal bleeding
-proliferative diabetic retinopathy
-hemorrhagic diathesis
-thrombocytopenia or platelet dysfunction
-esophageal varices
-aortic aneurysm
-SBP > 180 mm Hg or DBP > 110 mm Hg
-use of oral anticoagulants
-CPR in past six hours
-any IM injection in past six hours
-GI bleeding in the past two months
-organ biopsy, puncture of noncompressive vessel or major surgery within past two months
-intracranial trauma
-women of childbearing potential
-use of cocaine in past 24 hours
-allergy to aspirin

-use of any investigational drug within prior 30 days
-any other disease which would place a patient at undue risk

6.7 Dose: four dose arms were studied:
-rPA, a 15 MU single bolus
-rPA, a 10 MU bolus followed by a 5 MU bolus 30 minutes later
-rPA, a 10 MU bolus followed by a 10 MU bolus 30 minutes later
-tPA (alteplase) infused over 3 hours; 60% in first hour and 40% in the remaining two hrs

Aspirin (300-350 mg/day) was to begin prior to thrombolysis. Heparin, 5000 U as an IV bolus followed by an infusion at 1000 U/hr was to precede thrombolysis and was to be continued until the angiographic sheaths were removed 24 hours later. Heparin was not to be restarted.
rPA and tPA were to be weight-adjusted for low weight patients. For individuals weighing less than 65 kg and who are to receive the 10 + 10 dose of rPA, the dose was to be decreased to 8 + 8 MU. Individuals randomized to receive tPA and who weigh less than 65 kg were to receive 1.25 mg/kg tPA.

6.8 Objectives:

Primary objective:
-"to assess the effect of three dose regimens of rPA relative to the effect of a standard tPA dosing regimen on coronary artery patency 90 minutes after the initiation of thrombolytic therapy."

Secondary objectives:
-to assess the effect of the three dose regimens of rPA relative to tPA on:
-coronary artery patency 30 (optional) and 60 minutes (optional) after the initiation of thrombolysis
-coronary artery patency and reocclusion within 7 days
-left ventricular function 7 days after thrombolysis
-incidence of clinical endpoints (stroke, reinfarction, ischemia/angina and heart failure) and coronary interventions within one month after thrombolysis
-mortality rates at one and six months after thrombolysis
-hemostatic parameters during the first 48 hours after thrombolysis
-bleeding complications within the one month period after thrombolysis
-antibody formation within one month and six months after thrombolysis
-to evaluate the dose response relationships of rPA upon coronary artery patency, reocclusion, left ventricular function, clinical endpoints and safety.

6.9 Evaluations:

6.9.1 Arteriography: At 90 minutes, arteriography was to be performed in all patients to determine the extent of disease, TIMI grade of the infarct related artery (IRA), percent stenosis of the IRA, left ventricular ejection fraction and regional wall motion of the infarct zone. If possible, the IRA was also be visualized for TIMI grade and percent stenosis at 30 and 60 minutes after the initiation of thrombolysis. If the IRA remained closed at the 90 minutes angiogram, the patient was to be treated at the discretion of the investigator (PTCA). Repeat administration of rPA or tPA was not permitted. The use of intracoronary nitroglycerin was prohibited until after the 90 minute angiogram.

All patients were to have follow-up angiography several days after thrombolysis. TIMI grade and percent stenosis of the IRA, left ventricular ejection fraction and regional wall motion were to be assessed by the core angiographic laboratory. The USA and European protocols differed in the time of the follow-up arteriogram. In the USA (and the UK) the arteriogram was to be performed at 7 days. In Germany and Austria the protocol called for the arteriogram to be performed at discharge (the CRF mentioned 14-21 days)

6.9.2 Hemostatic tests: Fibrinogen, fibrin degradation products, plasminogen, and alpha-2 antiplasmin were to be measured at 2, 4, 8, 12, 24, and 48 hours after thrombolysis

6.9.3 Antibody to rPA was to be collected at baseline, one month and six months post thrombolysis.

6.9.4 Clinical Laboratory: Baseline clinical chemistry and hematology were to be obtained and repeat studies performed 72 hours after thrombolysis. Blood for CK and CK-MB was to be collected at baseline, 4, 8, 12, 24, 36 and 48 hours after thrombolysis.

6.9.5 Follow-up: In the USA, patients were to return at one month following thrombolysis for mortality assessment, antibody collection, adverse event (AE) reporting and coronary artery intervention assessment. In Europe these procedures were to be performed at discharge (implied to mean 14-21 days, based on the CRF). At six months blood was to be collected for antibody assay and mortality assessed in both the USA and Europe. Bleeds were classified as:

-mild--results in an estimated blood loss of less than 250 ml, no transfusion
-significant--results in an estimated blood loss of 250-500 ml, no transfusion
-major--results in an estimated blood loss > 500 ml and/or require transfusion and/or surgical intervention
-life threatening--any intracranial bleed, retroperitoneal bleed or any bleed causing hypotension.

Bleeds were also classified as to their severity by the sponsor, retrospectively, using information from the CRF. The CRF did not contain the referral to estimated blood losses. The CRF did require details of transfusion and blood pressure alterations. The clinical protocol provided certain specific definitions. Angina was defined as typical chest pain accompanied by ST segment alterations and resolution with sublingual nitroglycerin. Reinfarction was defined as typical chest pain not reversed by nitroglycerin and associated with EKG changes and CK-MB changes diagnostic of MI. Heart failure was defined as the presence of an S3 gallop and rales, or radiographic evidence of lung congestion or treatment of the signs or symptoms of heart failure with diuretics, digitalis or vasodilators. The CRF required strokes to be categorized according to whether they were hemorrhagic or nonhemorrhagic, whether they were fatal or nonfatal, and if nonfatal, whether they resulted in impairment (mild or moderate--can function independently, severe--cannot function independently). All patients were to have a CT scan within 24 hours of a stroke. The timing of the disability determination following a stroke was not stated in the clinical protocol. The CRF "suggest" the determination should be performed at the time of the stroke "completion."

6.10 Endpoints:

The primary endpoint was the 90 minute patency (TIMI 2 or TIMI 3 patency). The protocol stated that two-sided 95% CI were to be presented for the patency rates for each treatment group and two-sided 90% CI were to be presented on the difference in patency rates between the control group and each rPA dosage group. The study was powered (planned to enroll 150 patients per arm) "assuming that the underlying 90 minute patency rate was 80% such that this sample size provided 95% certainty that the observed difference in patency rates would be 6% or less. In addition, the sample size provided 98% certainty that equivalence to within 15 percentage points of the control would be concluded for at least one rPA dosage group if the groups were in fact equivalent."

Multiple secondary endpoints were planned in the clinical protocol. The variables for analyses included:

-patency (TIMI grade 2 or 3) on angiograms performed 30 and 60 minutes following thrombolysis and those performed at 7 days or discharge
-reocclusion
-left ventricular ejection fraction and regional wall motion analyses determined on the 90 minute and follow-up arteriogram
-clinical endpoints (stroke, reinfarction, CHF, angina), coronary artery interventions (PTCA, CABG), and bleeds within the one month after thrombolysis
-mortality at one and six months
-effect of hemostatic tests within 48 hrs of thrombolysis
-antibody formation at one and six months
-AE

6.11 Interim analyses:

The original clinical protocol stated "One to two interim analyses will be performed by the sponsor for the purpose of planning the large clinical efficacy trial. This interim analysis will be strictly for planning purposes and will not affect the conduct of the trial." Two interim analyses were actually performed by the sponsor for the purpose of selecting a dose for the clinical efficacy trial (INJECT). The results were available only to Boehringer Mannheim personnel. A Lan-DeMets group sequential procedure was used to adjust the final significance level of the equivalence hypothesis. This resulted in a final significance level of 0.049.

6.12 Results:

6.12.1 Patient Population: There were a total of 606 patients enrolled at 38 centers.

Table 42. RAPID-1 enrollment by Country

Countries	Germany	Austria	UK	USA	Total
Sites	13	1	2	22	38
Patients	266	6	18	316	606

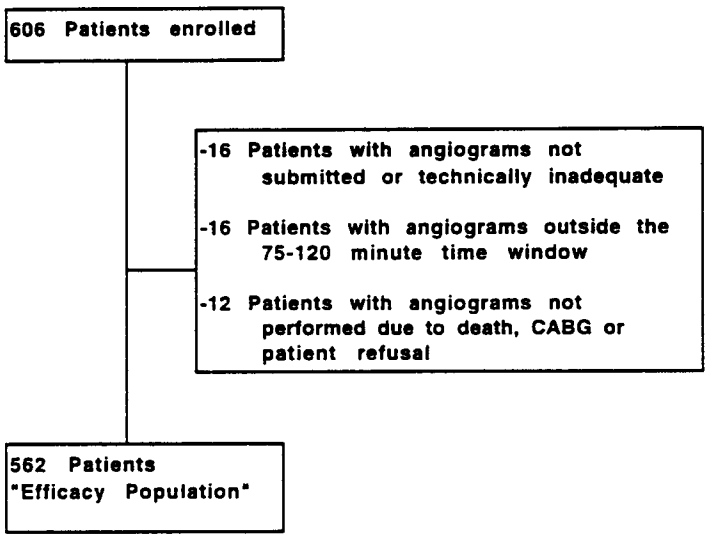

Figure 5. Disposition of Patients in RAPID-1

Not all patients had angiograms performed in the protocol-stated 90 minute time window (75-105 minutes). Nine patients had arteriograms performed between 105 and 120 minutes. Broadening the time window to 75-120 minutes allowed for the exclusion of a total of 44 patients. The sponsor analyzed the primary patency point per the protocol, but also summarized the data using the 90 minute time point window of 75-120 minutes.

The 44 excluded patients included patients randomized to:

-tPA	9 patients
-15 MU rPA	9 patients
-10 + 5 MU rPA	14 patients
-10 + 10 MU rPA	12 patients.

The 562 patients in the "efficacy population" are analyzed for all arteriographic endpoints. All patients are included in analyses of other outcomes.

6.12.2 Baseline Characteristics:

Of the 562 patients in the primary efficacy analysis:

Table 43. Randomization

Location	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA	Total
Europe	66	67	64	69	266
USA	79	70	74	73	296
Total	145	137	138	142	562

Of the 562 patients in the primary efficacy analysis:

Table 44. Characteristics:

Characteristic	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
Median age (range)	61 (33-76)	57 (29-82)	59 (35-75)	57 (25-75)
% Male	73	82	77	77
% Caucasian	88	90	93	93
Median weight, kg, (range)	80 (45-120)	80 (50-120)	84 (54-159)	79 (36-155)
Time from onset of pain to treatment > 6 hrs (%)	1	3	2	2
% Anterior infarction	45	49	49	50
% Prior MI	13	9	10	12
% Prior thrombolytic	4	2	1	3

•Reviewer's comment: Overall, the demographics of the patients were very similar to those in INJECT, except slightly more noncaucasians were enrolled (10% vs 1%) and almost all patients were treated within 6 hours of the onset of their symptoms.

6.12.3 Concomitant Medications: All but three patients received treatment with aspirin. All patients were treated with heparin. More than 70% of patients were still receiving heparin 24 hours after thrombolysis.

6.12.4 Protocol Deviations: Seven patients were enrolled despite the presence of exclusion criteria. One patient was entered into the study twice. He originally received tPA and reentered the study three months later and treated with 15 MU rPA. This patient was included as two separate patients in the evaluation of the data. Seven patients also received the wrong study medication due to an error in dosing. The results are presented based on the treatment received. Patients weighing less than 65 kg were to receive weight-adjusted doses of tPA or the 10 + 10 MU dose of rPA. 12 of 23 patients weighing less than 65 kg and randomized to the 10 + 10 MU rPA dose received the full dose. 12 of the 22 patients weighing less than 65 kg and randomized to tPA received the full tPA dose.

6.12.5 Primary Endpoint Analysis: Patency (TIMI grade 2 or 3) at 90 minutes was the primary endpoint. Overall, the mean and median times of the 90 minute angiograms were 90.4 and 90 minutes after the initiation of therapy, respectively. The protocol stated that only patients with angiograms

performed in the 75-105 minute time window would be included in the 90 minute endpoint analysis. Using the 75-105 minute time window and comparing each rPA dose to tPA for the primary null hypothesis ("The patency rate of the tPA group is > 15 percentage points higher than that of all rPA dosage groups, ie., not equivalent"), the resulting p-values were <0.001, 0.25, and 0.49 for 10 + 10 MU, 10 + 5 MU, and 15 MU rPA treatment groups, respectively. These results indicated that only the 10 + 10 MU treatment was possibly at least equivalent to the tPA treatment. These results were for the most narrow 90 minute time window. Similar results were obtained with broader windows, as shown below:

Table 45. % of Patients with Patency (TIMI 2 or TIMI 3) (%, 95% CI)

Time point	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
30 minute	53 (39-67)	48 (33-63)	60 (46-73)	60 (47-74)
n = 191 patients	n = 49 patients	n = 42 patients	n = 52 patients	n = 48 patients
60 minute	66 (57-76)	67 (57-77)	72 (64-81)	78 ‡(69-86)
n = 394 patients	n = 101 patients	n = 91 patients	n = 104 patients	n = 142 patients
90 minute (75-120 minute window)	77 (70-84)	63 (55-71)*	67 (59-75)**	85 (79-91)***
n = 562 patients	n = 145 patients	n = 137 patients	n = 138 patients	n = 142 patients

* < 0.01 p-value vs. tPA
** < 0.05 p-value vs. tPA
***P = 0.84, p-value vs. tPA
‡P = 0.08, p-value vs. tPA

Subgroup analyses performed by the sponsor showed that these results were the same regardless of location (USA vs. Europe), sex, age, weight, and time to treatment of patient subgroups.

The IRA was the right coronary artery in 261 patients (46%), the left anterior descending artery in 231 patients (41%) and the left circumflex artery in 63 patients (11%).

The sponsor analyzed patency (TIMI 2 or 3, above table) and, in a separate analysis, also examined TIMI3 patency, alone. The protocol stated that patency (implying TIMI 2 or 3) at 90 minutes was the primary endpoint.

Table 46. % of Patients with TIMI 3 Flow (%, 95% CI)

Time point	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
30 minute	27 (14-39)	21 (9-34)	31 (18-43)	31 (18-44)
n = 191 patients	n = 49 patients	n = 42 patients	n = 52 patients	n = 48 patients
60 minute	33 (24-42)	39 (29-49)	42 (33-52)	51 (41-61)*
n = 394 patients	n = 101 patients	n = 91 patients	n = 104 patients	n = 98 patients
90 minute	49 (41-57)	41 (33-49)	46 (37-54)	63 (55-71)**
n = 562 patients	n = 145 patients	n = 137 patients	n = 138 patients	n = 142 patients

* <0.01 p-value vs. tPA
** < 0.05 p-value vs. tPA

•Reviewer's comment: 70% of all patients with an early arteriogram had a 60 minute arteriogram. The performance of the 30 and 60 minute arteriogram was optional. The "optional" nature of these evaluations might imply some bias in the performance of the arteriograms. For example "sicker" patients (perhaps those with failure of thrombolysis) might not have the earlier arteriograms performed. The "optional" characteristic of the 30 and 60 minute arteriograms implies that these data should be interpreted as relatively subjective data with respect to the speed of thrombolysis.

6.12.6 Secondary Endpoints:

6.12.6.1 Patency at 30 Minutes: At the 30 minute time point there were no significant differences between any of the three rPA doses compared with tPA.

6.12.6.2 Patency at 60 Minutes: The protocol stated that "patency" would be examined at 30 and 60 minutes as secondary endpoints. The protocol did not say specifically whether patency (TIMI 2 or 3) would be examined separately from TIMI 3 patency. As the above tables illustrate, there was no significant difference in patency (TIMI 2 or 3) at 60 minutes.

At the 60 minute time point, the TIMI 3 rate was significantly higher for the 10 + 10 MU rPA group compared with the tPA group (51% vs. 33%, p = 0.009). The difference in patency rates (TIMI 2 + TIMI 3) was not significant at the 0.05 level of probability (p = 0.08, 78% vs. 66%).

•Reviewer's comment: The arteriographic analysis of TIMI used 90 minutes as the earliest time point measurement for patency. The patency rate for (3 hour infusion) tPA was 71% in TI MI. The RAPID 1 results are in accord with the TIMI patency results.

6.12.6.3 Patency/reocclusion at follow-up: Follow-up arteriography was performed at approximately 7 days in the USA and the UK, but at approximately 14-21 days in Germany and Austria. In the clinical protocol the definition of reocclusion required a follow-up arteriogram demonstrating the conversion of either TIMI 2 or 3 patency (at 90 minutes) to TIMI 0 or 1 grades. The follow-up arteriogram was performed a mean of 11 days, median of 8 days and a range of 1 to 44 days following thrombolysis. 493 patients (81%) had follow-up arteriograms.

Table 47. Patients with Patency (%, 95% CI) and reocclusion at follow-up

Endpoint	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
TIMI 3 Patency (n = 493 patients)	71% (63-79%) n = 123 patients	71% (63-79%) n = 124 patients	73% (65-81%) n = 123 patients	88%* (82-94%) n = 123 patients
TIMI 2 or TIMI 3 Patency (n = 493 patients)	88% (82-94) n = 123 patients	86% (79-92) n = 124 patients	81% (74-88) n = 123 patients	95% (91-99) n = 123 patients
Reocclusion (n = 359 patients with TIMI 2 or 3 on 90 minute arteriogram)	8% n = 90 patients	8% n = 78 patients	12% n = 86 patients	3% n = 105 patients

* < 0.001 p-value vs. tPA

An additional analysis of early patency was performed by the sponsor. In this analysis the number of occluded (TIMI 0 or 1) arteries that had been patent (TIMI 2 or 3) on earlier arteriograms were analyzed. This analysis is shown below:

Table 48. Patients with early closing of a patent IRA

Characteristic	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
Patients with patent IRA at 30 minutes	26	20	31	29
occluded at 60 minutes	0	1	0	0
Patients with patent IRA at 60 minutes	67	61	75	76
occluded at 90 minutes	2 (3%)	3 (5%)	6 (8%)	0 (0%)

•Reviewer's comment: These data suggest that the slightly earlier TIMI 3 patency induced by the 10 + 10 MU rPA dose may be maintained through the subsequent several days. The clinical significance of TIMI 3 patency vs. TIMI 2 + 3 patency is unknown. GUSTO -1 showed that TIMI 3 patency differed in respect to TIMI 2 patency primarily in the preservation of ventricular function. The mortality rates for patients with TIMI 2 vs. TIMI 3 patency were not significantly different in GUSTO-1. In RAPID-1, the slightly different reocclusion rates across the trial arms were not statistically different.

6.12.6.4 Coronary artery interventions during follow-up: During the 30 day follow-up period the number of coronary interventions were not significantly different across the treatment arms, as shown below:

Table 49. Coronary artery interventions

Intervention	tPA (n = 154)	15 MU rPA (n = 146)	10 + 5 MU rPA (n = 152)	10 + 10 MU rPA (n = 154)	Total (n = 606)
Number of patients with at least one intervention	97 (63%)	98 (67%)	114 (75%)	95 (62%)	404 (67%)
PTCA, early*	34 (22%)	35 (24%)	37 (24%)	23 (14%)	129 (21%)
PTCA, overall	78 (51%)	81 (56%)	87 (57%)	72 (47%)	318 (52%)
CABG, early*	0	1 (1%)	0	2 (1%)	3 (1%)
CABG, overall	16 (10%)	15 (10%)	24 (16%)	23 (15%)	78 (13%)
IC thrombolytic, early*	6 (4%)	6 (4%)	13 (9%)	4 (3%)	29 (5%)
IC thrombolytic, overall	9 (6%)	8 (6%)	19 (13%)	6 (4%)	42 (7%)
Atherectomy	7 (5%)	5 (3%)	5 (3%)	2 (1%)	19 (3%)
Other**	4 (3%)	3 (2%)	9 (6%)	8 (5%)	24 (4%)

*early--first six hours after initiation of thrombolysis
**Other--intraortic balloon pumps, intracoronary nitroglycerin, or stent placement

•Reviewer's comment: The above interventions did not differ significantly across the treatment arms. The much higher rate of interventions performed in RAPID-1 compared to INJECT may be related to the arteriographic strategy of RAPID-1, as well as performance at both USA and European sites.

6.12.6.5 Left ventricular performance: Ventriculography was to be performed at the 90 minute and follow up arteriographic examinations. However, less than 50% of patients had evaluable ventriculograms at 90 minutes (most European sites did not perform ventriculography, other reasons included inadequate contrast administration, arrhythmias, diaphragm motion). As shown below, there

was no significant difference between any of the three rPA arms and the tPA group. In the following tables, regional wall motion is expressed in units of standard deviation from the mean normal value.

Table 50. Left ventricular function at the early ventriculogram

LVF evaluation*	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
Ejection fraction				
mean ± SE	51.6 ± 1.4	50.8 ± 1.6	52.4 ± 1.4	49.8 ± 1.4
median	53.5	52.1	54	50.4
n (n = 275 total)	75	63	66	71
Regional wall motion				
mean	-2.65 ±0.14	-2.86 ± 0.13	-2.53 ±0.13	-2.55 ± 0.14
median	-2.94	-3.14	-2.66	-2.87
n (n = 262 total)	70	60	64	68

*P > 0.05 for comparison of each rPA dose to tPA

As shown in the table below, at the follow up angiographic visit, the mean ejection fraction and regional wall motion values were significantly better in the 10 + 10 MU rPA group than in the tPA group (p = 0.034 for ejection fraction and p = 0.02 for regional wall motion).

Table 51. Left ventricular function at the follow-up ventriculogram

LVF evaluation	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
Ejection fraction				
mean ± SE	49 ± 1.3	49.6 ± 1.4	53.2 ± 1.3*	52.9 ± 1.3*
median	51.4	52.5	54.3*	54.3*
n (n = 342 total)	84	80	87	91
Regional wall motion				
	-2.61 ± 0.13	-2.54 ± 0.12	-2.35 ± 0.12	-2.19 ± 0.12*
mean	-2.85	-2.70	-2.41	-2.34**
median ± SE	86	75	86	84
n (n = 348 total)				

* < 0.05 p-value vs. tPA
** < 0.01 p-value vs. tPA

•Reviewer's comment: Ventriculography appears more to be more technically constraining than coronary arteriography. In the GUSTO arteriographic study (NEJM 1993) only 40% of the enrolled patients actually had ventriculography performed--a rate comparable to RAPID-1. And, in GUSTO-1, the superior efficacy of accelerated dose tPA with respect to ventricular function was based on improvement in regional wall motion abnormality, since the overall ejection fractions did not differ significantly across the trial arms. Considering the spread of missing data across the trial arms of RAPID-1, and the historical precedent for technical difficulties, the RAPID-1 data appear to substantiate a claim of improved ventricular function following MI. The licensing for standard dose tPA was based upon documentation of ventricular function effects determined used radionuclide ejection fractions at 2-3 weeks following thrombolysis.

6.12.6.6 Mortality Rates: One month (approximately 30 day) follow-up data were available for 604 patients. Overall there were 26 deaths at the one month follow up point (4.2%). The average mortality rates were:

tPA 6/154 or 3.9%

15 MU rPA	6/146 or 4.1%
10 + 5 MU rPA	11/152 or 7.2%
10 + 10 MU rPA	3/154 or 1.9%.

There was no statistically significant difference in mortality rates. The 26 deaths included 3 deaths attributed to intracranial hemorrhage (2 in tPA arm and 1 in the 15 MU rPA arm). All other deaths were attributed to the underlying MI.

Six month mortality data were available for 85% (514) of the total enrolled patient population. Each of the treatment arms had approximately the same distribution of available data (83-85%). There was no statistically significant difference in mortality rates across the treatment arms.

Table 52. Mortality at six months

Result	tPA n = 154	15 MU rPA n = 146	10 + 5 MU rPA n = 152	10 + 10 MU rPA n = 154
% patients dead*	5.2	5.5	8.6	3.3
% patients dead**	6.2	6.4	10.2	3.8
% status unknown	16.2	14.4	16.5	13.6

*Patients with unknown status are assumed to be alive
**Patients with unknown status are not included in calculation of rate

Two patients in each of the treatment arms died between the short term follow-up date and the six month follow-up point.

6.12.6.7 Clinical Endpoints (reinfarction, congestive heart failure and angina): By 30 days, there were no significant differences in the rates between any of the rPA regimens and tPA for any of these three endpoints. The mean rates are shown below:

Table 53. % of Patients with reinfarction, congestive heart failure and angina

Endpoint	tPA	15 MU rPA	10 + 5 MU rPA	10 + 10 MU rPA
Reinfarction	4.5	6.2	4.6	2.6
Congestive heart failure	5.8	3.4	7.9	5.8
Angina	24.7	29.5	23	24.7

6.12.6.8 Relationship between 90 Minute TIMI Grade and Mortality: An analysis of mortality, based on TIMI grade, for all patients with early arteriograms (602 patients) is shown below:

Table 54. Mortality and TIMI grade

TIMI grade n	Mortality rate %
0 - 1 n = 164	8.5
2 n = 144	2.1*
3 n = 294	3.1**

* <0.05 p-value vs. TIMI 0-1
** <0.01 p-value vs. TIMI 0-1

•Reviewer's comment: These results are similar to the GUSTO-1 results which showed that mortality rates for patients with 90 minute TIMI 2 or 3 patency were significantly different from patients with TIMI 0 or 1. Like GUSTO-1, this study also shows that mortality rates for patients with TIMI 3 are not significantly different from patients with TIMI 2 patency at 90 minutes.

6.12.6.8 Strokes: There were a total of seven strokes by day 30. Six of the strokes were in the tPA arm (6 / 154 or 3.9%) and one was in the 15 MU rPA arm (1 / 146 or 1%). All patients underwent CT head scanning and hemorrhagic strokes were diagnosed in 4 of the 6 patients with strokes in the tPA arm as well as the one patient with a stroke in the 15 MU rPA arm.

6.12.6.9 Net Clinical Benefit: The net clinical benefit was defined by the sponsor in terms of the number or deaths and of nonfatal, disabling strokes that occurred in each group. These rates are shown below:

Table 55. % of Patients with death or nonfatal, disabling strokes

Treatment, n	Death or disabling stroke
tPA, 154 patients	4.5
15 MU rPA, 146 patients	4.8
10 + 5 MU rPA, 152 patients	7.2
10 + 10 MU rPA, 154 patients	1.9*

*P = 0.20

There were no statistically significant differences across the treatment arms.

•Reviewer's comment: The protocol and CRF did not state the time the disability evaluation should be performed. Therefore, it cannot be precisely stated that the disability determination was performed consistently at the 30 day follow-up period.

6.12.6.10 Bleeding Events: Hemorrhage was divided into categories based on the investigator's appraisal of the amount of blood loss and the need for hemorrhage. Bleeds were categorized as mild, significant, major or life-threatening. All patients in the major and life-threatening categories required transfusion. The patients with hemorrhages are summarized below in Table 56.

Table 56. Patients with bleeding events

Event	tPA (n = 154)	15 MU rPA (n = 146)	10 + 5 MU rPA (n = 152)	10 + 10 MU rPA (n = 154)
Number with at least 1 bleed	76 (49%)	56 (38%)	64 (42%)	75 (49%)
Number requiring transfusion (excluding surgery)	14 (9%)	10 (7%)	11 (7%)	21 (14%)
Bleeding site				
Catheter site	54 (35%)	37 (25%)	52 (34%)	56 (36%)
Gastrointestinal	11 (7%)	7 (5%)	12 (8%)	11 (7%)
Hematuna	11 (7%)	8 (6%)	9 (6%)	12 (8%)
Venipuncture site	9 (6%)	8 (6%)	4 (3%)	12 (8%)
Bleeding gums	8 (5%)	5 (3%)	5 (3%)	3 (2%)
Surgical bleeding	5 (3%)	6 (4%)	6 (4%)	10 (7%)
Intracranial	4 (3%)	1 (1%)	0	0
Retroperitoneal	3 (2%)	0	1 (1%)	1 (1%)
Intrathoracic	2 (1%)	0	0	0
Other puncture site	1 (1%)	0	3 (2%)	0
Site unknown	2 (1%)	1 (1%)	2 (1%)	3 (2%)
Other*	6 (4%)	11 (8%)	9 (6%)	15 (10%)

*includes hemoptysis, vaginal and rectal bleeding, bleeding on the extremities, bleeding from previous wounds, nose bleeding.

•Reviewer's comment: The transfusion-requiring bleed rate in INJECT was approximately 1% across all treatment arms. The corresponding transfusion- requiring bleed rate in RAPID-1 is approximately 10% and not statistically significantly different across the treatment arms. This difference may be attributed to multiple possibilities, but especially notable differences are the arteriographic evaluations in RAPID-1 and the inclusion of USA centers. The 10% transfusion rate in RAPID-1 compares to the approximately 6% transfusion rate in the arteriographic trial in GUSTO-1.

6.12.6.11 Hemostatic Parameters: The hemostatic parameters were measured by a core laboratory for the USA sites and by local hospitals for European sites. Compliance with testing was much lower in Europe, so most of the hemostatic data is from the USA. Approximately 50 patients had complete hemostatic data obtained. Following study agent administration, the decreases in mean fibrinogen levels were similar in the three rPA arms, and in each case the decrease was greater than that observed in the tPA group. The mean trough value was 26% of the mean baseline value in the 10 + 10 MU rPA group, compared with 43% in the tPA group. Complete return of fibrinogen levels to baseline had occurred by 48 hours after thrombolysis. All treatment arms (including the tPA arm) had similar decreases in mean plasminogen levels. At their nadir, mean plasminogen levels were approximately 20% of the baseline value. Likewise, the decrease in alpha-2 antiplasmin was the same for all treatment arms (to approximately 40% of the baseline value at the nadir). The increase in fibrin degradation products was similar in all treatment arms.

6.13 Safety Summary: The clinical laboratory values obtained in RAPID-1 were unremarkable. Additional AE are described below. The CRF did not emphasize the tracking for AE other than the suspected major safety concerns--heart failure and cardiovascular events, strokes and bleeds. The notable AE that occurred in more than 1% of rPA treated patients are listed.

Table 57. Patients experiencing additional AE
(exclusive of heart failure, bleeds, strokes, recurrent MI, deaths)

AE	tPA, n = 154 n (%)	15 MU rPA n = 146 n (%)	10 + 5 MU rPA n = 152 n (%)	10 + 10 MU rPA n = 154 n (%)
Back pain	33 (21%)	31 (21%)	32 (21%)	36 (21%)
Headache	17 (11%)	29 (20%)	20 (13%)	20 (13%)
Hypotension	20 (13%)	12 (8%)	14 (9%)	17 (11%)
Nausea	8 (5%)	9 (6%)	17 (11%)	17 (11%)
Ventricular tachycardia	18 (12%)	13 (9%)	17 (11%)	19 (12%)
Anxiety	17 (11%)	12 (8%)	18 (12%)	17 (11%)
Bradycardia	12 (8%)	9 (6%)	13 (9%)	10 (6%)
Fever	13 (8%)	9 (6%)	12 (8%)	14 (9%)
Shock	4 (3%)	4 (3%)	4 (3%)	3 (2%)
Ventricular extrasystoles	5 (3%)	9 (6%)	8 (5%)	10 (6%)
Ventricular fibrillation	5 (3%)	3 (2%)	6 (4%)	4 (3%)
Hypokalemia	7 (5%)	4 (3%)	6 (4%)	4 (3%)
Arthralgia	4 (3%)	5 (3%)	2 (1%)	5 (3%)
Abdominal pain	5 (3%)	3 (2%)	1 (1%)	0
Atrial fibrillation/flutter	3 (2%)	3 (2%)	0	4 (3%)
Pneumonia	2 (1%)	3 (2%)	4 (3%)	5 (3%)
Bundle branch block	2 (1%)	3 (2%)	1 (1%)	3 (2%)

6.14 RAPID-1 Summary and Reviewer's Comment: *RAPID-1 was an arteriographic study comparing 3 doses of rPA to a standard (3 hour) dose of tPA. Approximately 600 patients were enrolled with half of them in the USA. The 90 minute arteriogram showed that TIMI 3 patency was greater for the 10*

+ 10 MU rPA arm compared to tPA (51% vs. 33%, p < 0.05). The combined outcome of TIMI 3 or TIMI 2 patency for the 10 + 10 MU rPA arm was not statistically greater compared to tPA (85% vs 77%). The TIMI 3 (as well as TIMI 3 or TIMI 2) patency rates for the other two dose arms of rPA were lower than tPA. Left ventricular performance was evaluated by ventriculography in approximately 56% of the enrolled patients. The number of patients excluded from the ventriculogram assessment was evenly spread across the treatment arms. The follow-up ejection fraction and the wall motion index were significantly better for the 10 + 10 MU rPA arm. The mortality rates were not significantly different across the various treatment arms. Only seven strokes were recorded in the trial, with most of them in the tPA arm. Overall, these data suggest hat the 10 + 10 MU rPA dose was effective in coronary thrombolysis and preservation of ventricular function.

7.0 Detailed Review of RAPID-2:

7.1 Overview:

"A randomized, open label, multicenter, angiographic study to compare the effects of 10 + 10 MU r-PA (Reteplase) with front-loaded t-PA (Alteplase--Activase in USA, Actilyse in Germany) in patients with acute myocardial infarction (the RAPID 2 Study)." This study was conducted between November, 1993 and October, 1994 (last 35 day follow-up assessment) with the last 6 month follow-up assessment in March, 1995. A total of 324 patients were randomized to one of two trial arms--10 + 10 MU rPA or accelerated dose tPA (Alteplase/Activase). The primary endpoint was TIMI grade in the IRA at 90 minutes following thrombolysis. All rPA used in this trial was produced using the T2L promoter.

7.2 Investigators/Sites/Monitoring:

324 patients were enrolled at a total of 26 sites, 21 in the USA and five in Germany. 247 patients were enrolled in the USA (76%) and 77 (24%) were enrolled in Germany. The core angiographic laboratory was at the [redacted]. Monitoring of the clinical trial was performed by Boehringer Mannehim clinical research associates. No contract research organizations were involved in the clinical trial monitoring. The FDA inspected selected sites to verify protocol adherence and proper case report form record maintenance.

7.3 IRB/CF:

All studies were approved by the local IRB and/or ethics committees and all patients provided informed consent.

7.4 Design:

Open-label, randomized, multinational, multicenter, parallel group study comparing the safety and patency-effect of rPA (10 + 10 MU) to accelerated dose tPA. The original clinical protocol was dated September 10, 1993. The German and USA protocols and CRF were identical except for the administrative and regulatory details. There was one amendment (dated October 19, 1993). This amendment directed that:

- -CK and CK-MB blood tests would be obtained
- -exclusion criteria would include "previous Q wave myocardial infarction in the same area"
- -the window for the 30 minute arteriogram would be 30-44 minutes
- -minor administrative changes (spelling, telephone numbers).

No interim analyses were planned and none were performed. 150 patients were initially planned to be enrolled into each arm of the trial.

7.5 Inclusion Criteria:

- -ages 18 years and older
- -30 minutes of chest pain
- -persistent ST segment elevation ≥ 0.1 mV in 2 of 3 inferior leads, or ≥ 0.1 mV in leads I and aVL, or ≥ 0.2 mV in 2 contiguous precordial leads, or left bundle branch block
- -less than 12 hours since onset of chest pain

7.6 Exclusion Criteria:

-prior CABG
-prior stroke
-intracranial neoplasm, AV malformation or aneurysm
-active bleeding or known hemorrhagic diathesis
-SBP > 180 mm Hg or DBP > 110 mm Hg, that does not rapidly respond to treatment
-use of oral anticoagulants
-prolonged or vigorous CPR in past two weeks
-PTCA in past two weeks
-puncture of a non-compressible vessel in the past two weeks
-organ biopsy or major surgery in past three months
-active or potential internal bleeding, or any trauma within past three months
-pregnant or nursing women
-women of childbearing potential unless they have a negative pregnancy test
-inability to take aspirin
-any investigational drug within prior 30 days
-any disease which would place a patient at undue risk
-prior enrollment in this study

•Reviewer's comment: left bundle branch block was an exclusion criterion for RAPID-1. Patients with left bundle branch block were enrolled in INJECT. Otherwise the three trials (INJECT, RAPID-1 and RAPID-2) inclusion and exclusion criteria differed only in the allowable duration of time from onset of pain to treatment (12 hours in INJECT and RAPID-2, 6 hours in RAPID-1).

7.7 Dose:

-thrombolytics: 10 + 10 MU rPA (10 MU initially, followed in 30 minutes by 10 MU, both IV) vs. tPA delivered in an accelerated regimen (15 mg bolus, 0.75 mg/kg over 30 minutes, not to exceed 50 mg and 0.5 mg/kg over 60 minutes, not to exceed 35 mg, all IV, dose not to exceed 100 mg).

-aspirin: all patients were to receive 160-350 mg prior to thrombolysis and daily until discharge

-heparin: all patients were to receive a 5000 U IV bolus, followed by an infusion at 1000 U/hr (started prior to thrombolysis) for at least 24 hours. The duration of heparin use after 24 hours was at the discretion of the investigator. If heparin were used after 24 hours, the therapeutic goal was to maintain and aPTT of 2 times the control value.

7.8 Objectives:

Primary objective:

-"to assess the effects of a 10 + 10 MU rPA regimen relative to the effects of front-loaded alteplase regimen on TIMI grade at 90 minutes"

•Reviewer's comment: the assignment of "TIMI grade" as the primary endpoint implies that TIMI 3 and/or patency (TIMI 2 or 3) may be evaluated as the primary endpoint.

Secondary objectives:

-to assess the effects of rPA relative to the effects of tPA on:
-TIMI grade at 30 minutes, 60 minutes and 5 or more days after thrombolysis
-reocclusions that occur between the 90 minute arteriogram and the follow-up arteriogram
-ejection fraction and regional wall motion of the infarct zone at 90 minutes and at 5 or more days
-deaths within 35 days and 6 months
-clinical endpoints (CHF, reinfarction, angina, cardiogenic shock) within 35 days
-interventions (PTCA, CABG) within 35 days
-strokes within 35 days
-hemorrhages during hospitalization

-a composite outcome of any of the following : death, reinfarction, CHF, ejection fraction < 40% or less than 35% for patients with a prior MI

7.9 Evaluations:

7.9.1 Arteriography: Complete coronary arteriography was to be performed at 90 minutes in all patients to determine the extent of disease. Thirty minute and 60 minute arteriograms were also to be performed at the investigator's discretion. The original protocol stated that the following time windows would apply:

30 minutes--25-44 minute (should be performed after the second rPA bolus)
60 minutes--45-74 minute
90 minute--75-105 minute.

A ventriculogram was to be performed after the 90 minute arteriogram. No coronary interventions (including IC nitroglycerin) were to be used prior to the 90 minute arteriogram, unless the investigator felt a delay would result in undue risk or the patient was in cardiogenic shock. Interventions after the 90 minute arteriogram were at the discretion of the investigator. The original clinical protocol stated that all patients would have a follow-up arteriogram "unless it is not clinically indicated." This follow-up arteriogram was to be performed 5 days after thrombolysis unless the patient's clinical course required earlier performance. A ventriculogram was also to be performed after the follow-up coronary arteriogram.

7.9.2 Clinical Laboratory: Baseline hemoglobin and hematocrit were to be obtained and repeated daily, for three days. APTT was to be repeated daily X3 following thrombolysis. The protocol required the collection of no additional laboratory data.

7.9.3 Clinical Follow-up: During hospitalization, AE, cardiac interventions (CABG, PTCA) and clinical endpoints (reinfarction, CHF,angina, cardiogenic shock, death) were to be monitored. Patients were to be contacted at 35 days and at 6 months to determine their clinical status. At 35 days this assessment included mortality, clinical endpoints , coronary artery interventions and strokes. At 6 months, only mortality was to be assessed. A visit was not required for the follow-up data collection.

The clinical protocol contained multiple definitions. Reinfarction was defined) as an assessment made by the investigator based on the presence of at least two of the following:

-recurrent ischemic symptoms lasting > 30 minutes, after resolution of the symptoms of the index MI
-occurrence of new ST segment elevations or new Q wave
-a second elevation in cardiac enzymes to over the normal upper limit (or by a further 20% if already over the normal limit)
-angiographic reocclusion of a documented previously patent IRA.

Cardiogenic shock was defined in the protocol as a SBP < 90 mm Hg for at least one hour, not responsive to fluid resuscitation alone, thought to be secondary to cardiac dysfunction and associated with signs of hypoperfusion or cardiac index ≤ 2.2 L/minute/m^2. CHF was not explicitly defined in the protocol, but it was suggested that the diagnosis be based on signs or symptoms of congestion or low cardiac output. Recurrent ischemia was defined as the presence of symptoms, EKG changes and/or new pulmonary edema or murmur thought to represent myocardial ischemia. A stroke was defined as a new neurologic deficit resulting in death or lasting 24 hours. Strokes were to be categorized according to whether they were hemorrhagic or nonhemorrhagic, whether they were fatal or nonfatal and, if nonfatal, whether they resulted in physical impairment (mild or moderate--can function independently, or severe--cannot function independently). The protocol or CRF did not state the time of the disability determination. The CRF implied that the disability determination should be performed once the stroke is complete. Hemorrhages were to be classified as to site and severity. The sites included catheterization site, retroperitoneal, gastrointestinal, genitourinary, surgical, hematocrit or hemoglobin decrease (alone) or other. The severity was classified as:

mild-do not require transfusion; no hemodynamic compromise
moderate-require transfusion; no hemodynamic compromise
severe or life threatening-causes hemodynamic compromise.

Hemodynamic compromise was defined as decompensation in blood pressure from the baseline, usually to < 90 mm Hg systolic, that required blood or fluid replacement, inotropic support, ventricular assist, surgery or CPR to maintain sufficient cardiac output. The compromise must have been due to the

bleeding episode. The severity assessment was performed by the sponsor after the trial using information from the CRF. Causality for all serious AE was assigned by the sponsor using an algorithm included in the clinical protocol.

7.10 Endpoints:

7.10.1 Primary: The primary endpoint was TIMI grade at 90 minutes. To be included in this analysis, patients had to have an arteriogram performed in the 75-105 minute time window. The patency and TIMI 3 rates within each treatment group were to be compared. Comparisons of proportions between the two groups were to be made by two-sided Pearson's chi square tests at the 5% level of significance. One sided 95% lower CI were to be estimated on the difference between the tPA and rPA proportions. These bounds "were to represent the greatest difference from tPA to which rPA could be considered equivalent."

The trial was powered assuming that the underlying 90 minute patency (TIMI 2 and 3) and TIMI 3 rates for tPA were 85% and 60%, respectively. This would provide approximately 80% power to show a 9 percentage point difference in patency rates between rPA and tPA and a 14.5 percentage point difference in TIMI 3 rates between rPA and tPA.

7.10.2 Secondary: Secondary endpoints were to be analyzed by a comparison of proportions. These secondary endpoints included:

-TIMI grade at 30 minutes, 60 minutes and 5 or more days after thrombolysis
-reocclusions that occur between the 90 minute arteriogram and the follow-up arteriogram
-ejection fraction and regional wall motion of the infarct zone at 90 minutes and at 5 or more days
-deaths within 35 days and 6 months
-clinical endpoints (CHF, reinfarction, angina, cardiogenic shock) within 35 days
-interventions (PTCA, CABG) within 35 days
-strokes within 35 days
-hemorrhages during hospitalization
-a composite outcome of any of the following : death, reinfarction, CHF, ejection fraction < 40% or less than 35% for patients with a prior MI

7.11 Results:

7.11.1 Baseline Characteristics: There were a total of 324 patients enrolled at 26 centers. The demographics for all enrolled patients are shown below:

Table 58. Characteristics of all enrolled patients

Characteristic	10 + 10 MU rPA n = 169	tPA n = 155	P*
Age, median (range)	58 (24-87)	62 (30-89)	N/S
% Male	76	81	N/S
% Caucasian	90	91	N/S
Weight, median (range, kg)	82 (50-158)	82 (45-163)	N/S
Median time to treatment (hrs)	2.5	2.4	N/S
Time from symptom onset to treatment < 6 hrs (%)†	91	85	N/S
% Anterior MI	39	37	N/S
% Prior MI	17	8*	< 0.05
% Prior CHF	4	3	N/S
% Prior thrombolytic	4	4	N/S

* Chi-square test
†n = 168 rPA group

There was a statistically larger number of patients with a prior MI in the group randomized to rPA.

•Reviewer's comment: The 12.5% i overall incidence of prior MI is similar to the incidence in Rapid-1 and INJECT (12% and 14%, respectively). The other characteristics are also similar to those in RAPID-1 and INJECT.

7.11.2 Concomitant Medications: Only four patients failed to be treated with aspirin (two in each treatment arm). All patients were treated with heparin. 94% of the patients randomized to rPA and 88% of the patients randomized to tPA were still receiving heparin at the end of 72 hours (the difference is not statistically significant). At study entry, there was no statistically significant difference in the number of patients being treated with various medications (beta blockers, ace inhibitors, digoxin, nitrates, etc.) between the two treatment arms.

7.11.3 Protocol Deviations: Nine patients were enrolled despite meeting exclusion criteria. Three of these patients did not have an MI and three of these patients had the onset of their symptoms more than 12 hours prior to treatment. The other deviations related to a prior stroke, prior CABG, and unknown time of symptom onset. There were four dosing errors in which patients did not receive their assigned medication. All four patients were randomized to receive tPA, but received rPA. The sponsor analyzed all patients according to the medication they received.

7.11.4 Primary Endpoint Analysis: TIMI grade at 90 minutes was the primary endpoint. The mean and median times of the 90 minute arteriogram were 90 and 90 minutes after the initiation of therapy. 32 patients did not have arteriograms performed within the prestated window (75-105 minutes) defining the 90 minute arteriogram. However, 98% of the patients had arteriograms performed at some point early in their hospital course, as shown below:

Table 59. Time windows for 90 minute arteriogram

Number of patients with arteriograms performed in each time window	10 + 10 MU rPA n = 169 patients	tPA n = 155 patients
in 75-105 minute window	149 (88%)	143 (92%)
in 75-120 minute window	157 (93%)	146 (94%)
any time during the early catheterization	166 (98%)	153 (99%)

The protocol stated that the primary analysis would be limited to patients with arteriograms performed in the 75-105 minute time window. The sponsor performed this analysis, but also analyzed the results using the two other early time windows. The statistical analyses across these three populations revealed similar findings, as shown below:

Table 60. % of patients with various TIMI grades at 90 minute time windows

Arteriographic time window	TIMI 3		TIMI3 or TIMI 2	
	rPA	tPA	rPA	tPA
75-105 minutes	60*	45	85**	73
75-120 minutes	60**	45	83**	73
any early arteriogram	59*	44	82**	71

* < 0.01 p-value vs. tPA
** < 0.05 p-value vs. tPA

The sponsor chose to analyze the patients with arteriograms performed in the 75-120 minute time

window further, since more patients would be included in the analysis and a similar analysis was performed for RAPID-1. The 30, 60 and 90 minute patency and TIMI 3 results for this group are shown below.

Table 61. Patients with Patency ("TIMI 2 or TIMI3" and TIMI 3) at time points, % and 95% CI (75-120 minute time window)

Time point	TIMI 3		TIMI 3 or TIMI2	
	rPA	tPA	rPA	tPA
30 minutes (n = 96)	27 (16-39) n = 55	39 (24-54) n = 41	67 (55-80) n = 55	66 (51-80) n = 41
60 minutes (n = 236)	51 (42-60)** n = 121	37 (29-46) n = 115	82 (75-89)* n = 121	66 (57-75) n = 115
90 minutes n = 303	60 (52-68)** n = 157	45 (37-53) n = 146	83 (78-89)** n = 157	73 (66-81) n = 146

*<0.01 p-value vs. tPA
**<0.05 p-value vs. tPA

Similar results were obtained in the subgroup analysis of Germany vs. USA. The tests for interaction between location and treatment group were not significant (p = 0.44 for patency and p = 0.15 for TIMI 3).

The results of analyses of patency and TIMI 3 by various subgroup characteristics showed that only time to treatment resulted in a statistically significant difference for medication effect in each treatment arm. The sponsor performed the following subgroup analyses for the main treatment effect as well as the treatment effect interaction within the subgroup (eg., men vs. women).

Table 62. Results of significance tests for main effect and interaction in subgroups

Signifi-cance test	Sex	Age	Weight	IRA	Time to treatment
Patency					
Main effect	p = 0.83	p = 0.50	p > 0.99	p = 0.19	p = 0.002
Interaction	p = 0.48	p = 0.59	p = 0.40	p = 0.71	p = 0.96
TIMI 3					
Main effect	p = 0.81	p = 0.72	p = 0.86	p = 0.82	p = 0.12
Interaction	p = 0.76	p = 0.82	p = 0.75	p = 0.48	p = 0.70

•Reviewer's comment: The finding that patency was related to the time to treatment (for both tPA and rPA) is consistent with the results from other arteriographic trials. The subgroup analyses, while involving relatively small numbers of patients, revealed no signals for concern.

Additionally, the analysis of subgroups based on the presence of a history of prior MI revealed no difference in main effect outcome (n = 25 patients in rPA group and n = 12 patients in tPA group).

•Reviewer's comment: Regardless of the time window selected for analysis of the 90 minute arteriogram, the number of patients with patency or TIMI 3 flow was greater in the rPA arm than in the tPA arm. These results were consistent across the sites enrolling the largest numbers of patients.

Of the 324 patients enrolled, 73% had 60 minute arteriograms and 30% had 30 minute arteriograms. As with RAPID-1 , this "optional" arteriographic endpoint may be affected by bias. The results from these early time points should be viewed subjectively and do no t document earlier clot lysis by rPA compared to tPA.

In GUSTO-1 90 minutes was the earliest time point measurement for patency. At 90 minutes the accelerated tPA TIMI 3 flow rate was 54%. This may be compared to the 45% TIMI 3 flow rate detected in RAPID-2. The patency (TIMI 2 or 3) rate in GUSTO was 81% at 90 minutes in GUSTO. This may be compared to the 73% patency rate detected in RAPID-2. The reason for the somewhat lower TIMI 3 and patency rates for accelerated tPA are not obvious

7.11.5 Secondary Efficacy Analyses:

7.11.5.1 Patency and TIMI 3 at 30 Minutes: Only 30% (96) of the enrolled patients had arteriograms performed at 30 minutes. There was no statistically significant difference in patency or TIMI 3 grade.

7.11.5.2 Patency and TIMI 3 at 60 Minutes: 73% (236)of the enrolled patients had arteriograms performed at 60 minutes. The mean and median times for performance of the arteriogram were 62 and 60 minutes, respectively.

7.11.5.3 Patency and TIMI Grade 3 Rates at the Follow-up Arteriogram: 74% (241) of the enrolled patients had follow-up arteriograms. The mean and median times for performance of the arteriogram were 6.4 and 5 days, respectively. The range for performance of the arteriogram was from the day of treatment to 30 days post thrombolysis.

•Reviewer's comment: An arteriogram was to be performed prior to the recommended 5 day time point if the patient developed symptoms necessitating an arteriographic evaluation. If a patient had more than one follow-up arteriogram, the lowest TIMI grade was included in the analysis for the follow-up effect.

A follow-up arteriogram was not completed for 41 patients in the rPA group and 42 patients in the tPA group for the following reasons:

Table 63. Patients without a follow-up arteriogram

Reason for no follow-up arteriogram	rPA	tPA
CABG	18	11
Death	4	10
Physician discretion	9	4
Patient refused	3	8
AE	5	3
Other	2	6
Total	41	42

Table 64. Patency and TIMI 3 rates at follow-up arteriogram (%, 95% CI)

Rate	10 + 10 rPA (n = 128 patients)	tPA (n = 113 patients)
Patency (TIMI2 or TIMI 3)	89 (84-95)	90 (85-96)
TIMI 3	75 (68-83)	77 (69-85)

There was no statistically significant difference in patency or TIMI 3 grade at follow-up.

7.11.5.4 Reocclusion Rates: Reocclusion was defined as a patent IRA (TIMI 2 or TIMI 3) at the 90 minute arteriogram and a nonpatent artery (TIMI grade 0 or 1) at any follow-up evaluation. Of the 241 patient with follow-up arteriograms, 197 (82%) had patency assigned on the early arteriogram. Of these patients, 16 had reocclusions (10 in the rPA group and 6 in the tPA group). The corresponding reocclusion rates were 9% for rPA and 7% for tPA (p = 0.61).

•Reviewer's comment: These reocclusion rates are similar to those demonstrated in RAPID-1, where 81% of the enrolled patients had follow-up arteriograms and the reocclusion rates were 8% and 3% for tPA and rPA, respectively.

The sponsor performed an additional analysis of early closure. In this analysis the sponsor determined the percentage of patients with patent (TIMI 2 or 3) IRA at 30 minutes that were nonpatent (TIMI 0 or 1) at 60 minutes and those with patent arteries at 60 minutes that were nonpatent at 90 minutes.

Table 65. Patients with early closing of a patent IRA

Result	10 + 10 rPA	tPA
Patients with patent IRA at 30 minutes	37	27
occluded at 60 minutes	0	0
Patients with patent IRA at 60 minutes	99	76
occluded at 90 minutes	1 (1%)	4 (5%)

7.11.5.5 Coronary Artery Interventions within 35 Days of Thrombolysis: In this analysis the number of coronary interventions (PTCA, CABG, additional systemic thrombolytic administration, atherectomy, intracoronary nitroglycerin administration) were tracked over the 35 day follow-up period. Overall 69% of the enrolled patients had at least one of these interventions. In a comparison of the two agents, there was no significant difference in any of these procedures or the total number of procedures over the 35 days. There were significantly fewer procedures performed in the rPA group during the first six hours after thrombolysis.

Table 66. Summary of coronary artery interventions

Intervention*	10 + 10 rPA (n = 169 patients)	tPA (n = 155 patients)
Number of patients with at least one intervention	112 (66%)	110 (71%)
PTCA of the IRA		
early**	21 (12%)	37 (24%)
overall	89 (53%)	89 (57%)
CABG		
early	0	1 (1%)
overall	22 (13%)	15 (10%)
Additional thrombolytic		
early	3 (2%)	6 (4%)
overall	7 (4%)	13 (8%)
Atherectomy of IRA		
early	0	1 (1%)
overall	7 (4%)	6 (4%)
IC nitroglycerin		
early	11 (7%)	18 (12%)
overall	38 (23%)	43 (28%)
Other***		
early	3 (2%)	3 (2%)
overall	8 (5%)	8 (5%)

*only interventions of the IRA

**early--within the first six hours after thrombolytic administration

***other--stent placement, intraortic balloon pumps, rotoblator therapy, laser angioplasty, crossing the lesion with a wire

64 patients underwent coronary interventions within the first six hours following the administration of the study thrombolytic. During this "early" period, 23 patients in the rPA group underwent interventions (13.6%) and 41 patients in the tPA group underwent interventions (26.5%;p < 0.01 rPA vs. tPA).

7.11.5.6 Ventricular Function: Ventricular function was assessed by the ejection fraction and regional wall motion estimates provided by the early and follow-up ventriculograms.

The protocol called for patients to have ventriculograms performed with the 90 minute arteriogram. Because of multiple factors (patient condition, technical inadequacies, arrhythmias) 97 patients (30%) did not have evaluable ventriculograms performed with their early catheterization and 165 patients (51%) did not have evaluable ventriculograms performed in follow-up. Of the 46 patients without an early ventriculogram performed, 22 were in the rPA arm and 24 were in the tPA arm. Of the 47 patients without the performance of a follow-up ventriculogram, 23 were in the rPA arm and 24 were in the tPA arm. Of the 57 patients with technically inadequate early ventriculograms, 27 patients were in the rPA arm and 30 were in the tPA arm. Of the 35 patients with technically inadequate follow-up ventriculograms, 18 were in the rPA arm and 17 were in the tPA arm. Overall, the missing ventriculograms were evenly divided between the two arms of the trial.

Table 67. Left ventricular function

LVF evaluation	10 + 10 MU rPA	tPA	P*
Early:			
Ejection Fraction (%) mean ± SE median n	 52 ± 1 54 123	 53 ± 1 55 104	0.72
Regional wall motion** mean ± SE median n	 -2.53 ± 0.08 -2.69 117	 -2.76 ± 0.10 -2.85 98	0.07
Follow-up:			
Ejection Fraction (%) mean ± SE median n	 52 ± 1.2 54 89	 54 ± 1 54 77	0.25
Regional wall motion mean ± SE median n	 -2.28 ± 0.11 -2.31 87	 -2.29 ± 0.11 -2.29 72	0.96

*t test

**Regional wall motion is expressed in units of standard deviation from the mean normal value.

The sponsor utilized all the available ventriculogram data (ventriculogram result at any "early" time point and any follow-up time point) to examine ventricular function. There was no statistically significant difference in ejection fraction or regional wall motion abnormality between the two study arm patient populations.

•Reviewer's comment: While RAPID-1 showed a statistically significant improvement in ejection fraction and regional wall motion at follow-up, RAPID-2 did not detect a difference. There were a few more patients (total of 173 patients) evaluated at the follow-up time point in RAPID-1 compared to RAPID-2 (total of 166 patients) and perhaps the slightly different sample size may have influenced the results.

7.11.5.7 35 day Mortality: There were 20 deaths within the 35 day follow-up period (7 in the rPA group and 13 in the tPA group). The mortality rates were 4% and 8% for rPA and tPA, respectively (p = 0.11). 19 of the 20 deaths were related to the underlying cardiac disorder (10 patients died in cardiogenic shock, other causes were ventricular rupture, asystole, ventricular arrhythmia). One death (patient treated with tPA) was related to an intracranial hemorrhage. Follow-up data were available for all enrolled patients.

7.11.5.8 Six Month Mortality: 14 patients (4% of the enrolled population) did not have six month follow-up mortality data (5 patients in rPA arm and 9 patients in tPA arm). By six months there were a total of 25 deaths recorded (3 deaths in the rPA arm and 2 deaths in the tPA arm, after 35 days). Overall, the six month mortality rate for rPA was 6% and for tPA was 10% (regardless of whether patients with unknown status are assumed to be alive or not included in the calculation, P > 0.05).

7.11.5.9 Clinical Endpoints (cardiogenic shock, CHF, reinfarction, angina) within 35 Days: There were no statistical difference in the rates of the four clinical endpoints between the two arms of the trial. The point estimates are shown below.

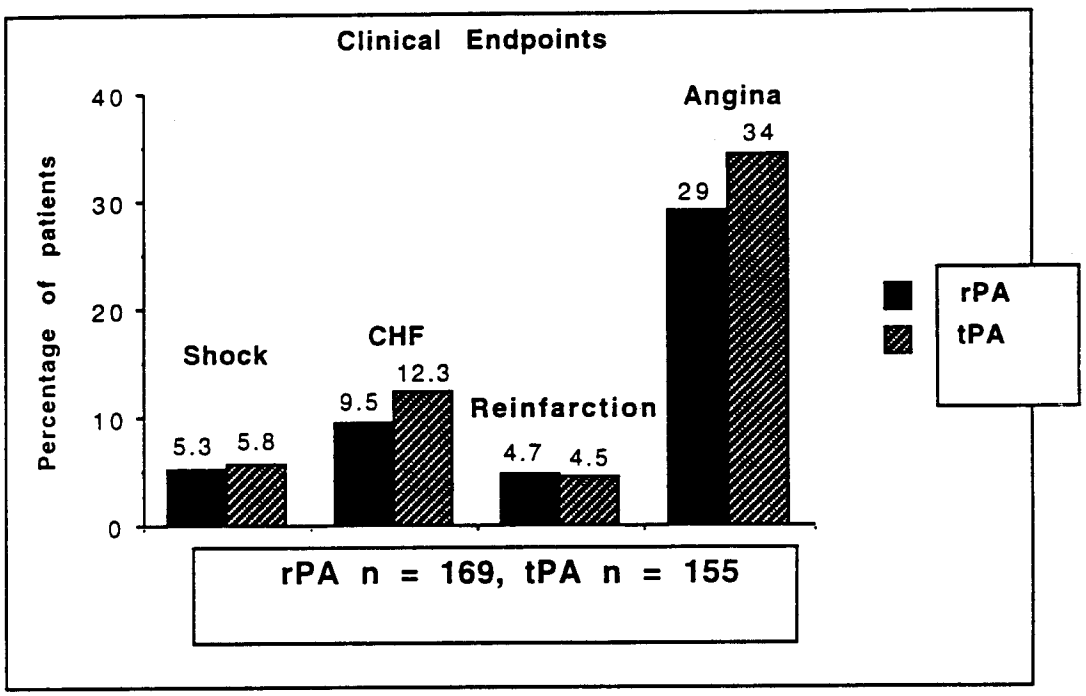

Figure 6. RAPID-2 Endpoints

•Reviewer's comment: In neither RAPID-1 or RAPID-2 was there a statistically significant difference in the incidence of CHF. The incidence of CHF was slightly higher in RAPID-2 (10-12%) than in RAPID-1 (approximately 6%).

7.11.5.10 Relationship between 90 Minute TIMI Grade and Mortality: There was a significant relationship between mortality and TIMI grade. Patients with tIMI 3 flow had a significantly lower mortality rate in comparison with patients with TIMI 0-1 flow (p = 0.02).

Table 68. Summary of mortality by 90 minute TIMI grade

Patients	TIMI 0-1	TIMI 2	TIMI 3
n	n = 74	n = 79	n = 166
Mortality rate (%)	12	3.8*	4.2**

* p = 0.05 TIMI 2 vs TIMI 0-1
** p = 0.02 TIMI 3 vs TIMI 0-1

•Reviewer's comment: These findings are similar to those from RAPID-1, as well as other arteriographic thrombolytic studies.

7.11.5.11 Strokes within 35 Days: There were a total of seven patients who suffered strokes, three in the rPA group and four in the tPA group. One stroke was lethal before a CT scan of the head could be obtained. Five of the remaining strokes were of the hemorrhagic type and one was nonhemorrhagic (patient treated with rPA). The stroke rates were 1.8% and 2.6% for rPA and tPA, respectively (p = 0.71). Only one patient suffering a stroke was able to function independently by day 35 of follow-up.

7.11.5.12 Bleeding during Hospitalization: Bleeds were classified by site and severity. A total of 149 patients (46%) experienced at least one bleeding episode. 36 of the patients required transfusion (11%). The incidence of bleeding events did not statistically differ between the patients in the two arms of the study.

Table 69. Summary of patients with hemorrhages

Event	10 + 10 MU rPA (n = 169)	tPA (n = 155)
Number with at least one hemorrhage	76 (45%)	73 (47%)
Mild*	62 (34%)	62 (37%)
Moderate	19 (10%)	17 (10%)
Severe	8 (4%)	5 (3%)
Number requiring transfusion (excluding surgical transfusion)	21 (12%)	15 (10%)
Number requiring transfusion (excluding surgical transfusion or puncture site hemorrhage)	9 (5%)	5 (3%)
Retroperitoneal	2 (1%)	2 (1%)
Gastrointestinal	9 (5%)	10 (7%)
Genitourinary	9 (5%)	9 (6%)
Surgical bleeding	9 (5%)	8 (5%)
Puncture site	65 (39%)	54 (35%)
Site unknown	3 (2%)	0
Other**	16 (10%)	15 (10%)

*patients may have had multiple hemorrhages of different severity
**includes gum, nose and mouth bleeding, hemoptysis, bruising on the extremities, drop in hemoglobin, infraclavicular bleed, bleeding from previous wounds

•Reviewer's comment: 21 patients in the rPA group and 20 patients in the tPA group weighed less than 65 kg. The hemorrhage rate in the two groups was comparable (52% of rPA-treated patients had at least one hemorrhage and 24% required transfusion; 80% of the tPA-treated patients had at least one hemorrhage and 30% required transfusion). The number of patients requiring transfusion in RAPID-2 (10-12%) is similar to the number in RAPID-1 (9-12%). .

7.11.5.13 Net Clinical Benefit: The rate of deaths + disabling strokes was not significantly different between the two treatment arms (5% rPA vs. 9% tPA, p = 0.19).

7.11.5.14 Composite Endpoint of Death, Reinfarction, CHF, Shock or a Follow-up Ejection Fraction of <40% (or<35% in patients with prior MI): If a patient had more than one of these possible outcomes within the 35 days of follow-up, he was included only once in the total for the "worst" outcome, as defined by the order of events in the table below:

Table 70. Patients with a composite endpoint within 35 days

Endpoint	10 + 10 MU rPA (n = 169)	tPA (n = 155)
Death	7	13
Reinfarction	5	3
CHF or shock	14	16
Ejection fraction decreased*	10	3
Total number of patient with one of the above	36 (21%)	35 (23%)**

*166 patients had a follow-up ventriculogram
**P = 0.78 rPA vs. tPA, Chi-square test

7.12 Safety Summary: Like RAPID-1, the CRF for RAPID-2 did not emphasize the tracking for AE other than the suspected major safety concerns--heart failure and cardiovascular events, strokes and bleeds. The notable AE that occurred in more than 1% of rPA treated patients are listed below.

Table 71. Patients experiencing additional AE
(exclusive of heart failure, bleeds, strokes, recurrent MI, deaths)

AE	10 + 10 rPA (n = 169)		tPA (n = 155)	
	n	%	n	%
Back pain	48	28.4	39	25.2
Hypotension	42	24.9	41	26.5
Ventricular tachycardia	36	21.3	27	17.4
Headache	31	18.3	26	16.8
Nausea	23	13.6	23	14.8
Fever	21	12.4	17	11.0
Anxiety	13	7.7	9	5.8
Supraventricular tachycardia	10	5.9	7	4.5
Atrial fibrillation/flutter	13	7.7	9	5.8
Dyspepsia	11	6.5	7	4.5
Ventricular fibrillation	10	5.9	4	2.6
Arthralgia	8	4.7	7	4.5
Asystole	6	3.6	6	3.9
Third degree heart block (treated)	7	4.1	7	4.5
Second degree heart block (treated)	5	3.0	2	1.3
Urinary retention	5	3.0	2	1.3
Oliguria	4	2.4	2	1.3
Confusion	3	1.8	3	1.9
Abdominal pain	3	1.8	2	1.3
Electromechanical dissociation	2	1.2	6	3.9
Constipation	2	1.2	2	1.3
Sepsis	1	0.6	2	1.3
Urticaria	1	0.6	2	1.3

7.13 *Summary of RAPID-2 and Reviewer's Comment:* *RAPID-2 was a comparison of accelerated dose tPA to the 10 + 10 MU dose of rPA in 324 patients. Most of the patients were in the USA. As with RAPID-1, only 10% of patients were noncaucasian. 166 patients were randomized to rPA and 155 patients were randomized to tPA. The primary endpoint was patency at 90 minutes. RAPID-2 provided patency results consistent to those from RAPID-1. Patency (TIMI2 or 3) was 83% for the rPA group and 73% for the tPA group at 90 minutes. TIMI 3 grade was 60% for the rPA group and 45% for the tPA group. The results were statistically significant for the difference (rPA - tPA). These patency results are similar to those obtained in RAPID-1. Unlike RAPID-1, follow-up ventriculograms demonstrated no difference in the ejection fraction or regional wall motion abnormalities between the two arms of the trial. However, ventricular performance measures were very similar and the combined data from RAPID-1 and RAPID-2 suggest that ventricular performance after treatment with rPA is no worse than after treatment with tPA. Like RAPID-1, the mortality rates for the treatment arms in RAPID-2 (4-8%) were lower than those in INJECT (9-9.2%). Also like RAPID-1, there was no statistical difference in the number of strokes between the patients in the treatment arms. Overall, these two studies are consistent in their results and substantiate that coronary thrombolysis by the 10 + 10 MU rPA dose appears no worse than that by tPA.*

8.0 Safety Summary from Phase 3 Studies:

The incidence of stroke and mortality in the RAPID studies is too low in comparison to INJECT to be of significance. However, of special note is the incidence of reporting of hemorrhages in the USA versus Europe. The incidence of bleeding events based on hemorrhage site and location of the study are shown in Table 71.

Table 72. Hemorrhage Rates by Clinical Trial Site

Bleeding site	INJECT	RAPID-1 and RAPID-2	
	Europe n = 2,965	Europe n = 113	USA n = 210
Injection site*	4.6%	19.5%	48.6%
Gastrointestinal	2.5%	1.8%	9.0%
Genitourinary	1.6%	0.9%	9.5%
Anemia, site unknown	2.6%	0.9%	1.4%

*includes the arterial catheterization site (all patients in the RAPID studies underwent arterial catheterization)

9.0 Reviewer's Comments Regarding Clinical Studies: *The phase 3 studies support the safety and efficacy of Retaplase in the treatment of AMI. In general, these study show that Reteplase is no worse than SK with respect to 35 day mortality. The patency studies also show that the coronary thrombolytic effect of Reteplase is comparable to that of tPA. These studies do not establish that Reteplase is equivalent to streptokinase or tPA. The results from the GUSTO-3 study will help establish the definitive role of Reteplase in the management of AMI.*